A Randomized Controlled Trial of Fluid Supplementation in Term Neonates with Severe Hyperbilirubinemia with N/3 (0.3%) Saline in 5% Dextrose.

Dissertation Submitted to

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In partial fulfillment of the regulations

For the award of the degree of

D.M. (NEONATOLOGY)

2010 – 2013

MADRAS MEDICAL COLLEGE

THE TAMIL NADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI

INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
Dr. Mohamed Sajjid
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Dear Dr. Mohamed Sajjid

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "A Randomized Controlled Trail of Fluid Supplementation in Term Neonates with Severe Hyperbilirubinemia with N/3 (0.3%) saline in 5% Dextrose"" No.34042012.

The following members of Ethics Committee were present in the meeting held on 19.04.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2.	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member Secretary
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9.	Thiru. S. Govindsamy. BABL	-- Lawyer
10.	Tmt. Arnold Soulina MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

CERTIFICATE

This is to certify that the dissertation entitled "**A Randomized Controlled Trial of Fluid Supplementation in Term Neonates with Severe Hyperbilirubinemia with N/3 (0.3%) Saline in 5% Dextrose"** is a bonafide work done by **Dr. MOHAMED SAJJID** during the period between APRIL 2012 – MARCH 2013 towards the partial fulfillment of requirements for the award of D.M. (NEONATOLOGY) degree for which examination is to be held in August 2013 by The Tamilnadu Dr.M.G.R. Medical University, Chennai.

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DECLARATION

I solemnly declare that the dissertation entitled "**A Randomized Controlled Trial of Fluid Supplementation in Term Neonates with Severe Hyperbilirubinemia with N/3 (0.3%) Saline in 5% Dextrose"** is the original work done by me at the Institute of Child Health and Hospital for Children and Institute of Obstetrics and Gynaecology and Hospital for Women and Children, Egmore, Chennai during the D.M. course (2010-2013), under the guidance and supervision of Prof. Dr. J .Kumutha, Professor and H.O.D. of Neonatology. The dissertation is submitted to **THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY** towards the partial fulfillment of requirement for the award of **D.M. (Neonatology).**

Place: Chennai. (Dr. MOHAMED SAJJID)

Date:

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CONTENTS

INTRODUCTION

Hyperbilirubinemia is a very common problem in the neonates with an overall incidence of 70-80% (1). It occurs due to the deposition of bilirubin released from breakdown of RBCs and from other non-heme sources in the skin and mucus membranes of the newborn. It is more common in preterm babies than full term newborns (2). In the majority of cases jaundice is mild and transient. 5-10% of the newborns develop clinically significant jaundice requiring intervention (3). Neonatal jaundice remains one of the most common reasons for readmission to hospital during the first week of life (4).

Bilirubin Biochemistry (Diagram 1):

Bilirubin is produced by a two-stage catabolism of haem in the reticuloendothelial system. The majority of haem is produced from the turnover of haemoglobin released from naturally decommissioned or pathologically destroyed erythrocytes. Haem (ferroprotoporphyrin IX) has a porphyrin ring structure which is opened by haem oxygenase. The intermediate pigment, biliverdin, is water-soluble, non-toxic and serves as the excretory product of haem in amphibians, reptiles and birds. In mammals, reduction of biliverdin by biliverdin reductase results in the production of bilirubin. Bilirubin is an antioxidant in the body and but is neurotoxic at high levels (5).

Bilirubin Metabolism and Excretion (Diagram 2):

In the newborn baby bilirubin is produced mainly from the breakdown of red cells, with up to a quarter resulting from ineffective erythropoiesis and other haem-containing compounds, such as myoglobin and cytochromes. Bilirubin is transported in the blood bound reversibly to serum albumin on high and low affinity sites, with a potential molar bilirubin to albumin ratio of up to 3:1. Under normal circumstances, the amount of free bilirubin circulating in the jaundiced newborn is very low.

Conjugation of bilirubin with glucuronic acid occurs in the smooth endoplasmic reticulum to form water-soluble mono and diglucuronides of bilirubin in the liver. These reactions are catalysed by the microsomal hepatic enzyme uridine diphosphoglucuronosyl transferase (UDPGT). Conjugated bilirubin in the form of monoglucuronide, which is more predominant form in the newborn, and diglucuronide is actively transported out of the liver cell and enters the biliary canaliculi as a component of the bile.

In adults, most of the conjugated bilirubin is converted by colonic flora to urobilinogen before elimination in the stool as stercobilinogen. In the newborn, a significant amount is hydrolysed by β-glucuronidase in the small gut to yield unconjugated bilirubin, which can re-enter the circulating pool via the enterohepatic circulation.

The Normal Pattern of Neonatal Jaundice:

The fetus excretes unconjugated bilirubin via the placenta and maternal liver. In the absence of fetal hyperbilirubinaemia or maternal liver disease, the mean bilirubin level in umbilical cord blood at birth is 1-2 mg/dL. Jaundice in the newborns can be physiological or pathological depending upon the level and the cause.

Physiological Hyperbilirubinemia:

It is the jaundice that is attributable to physiological immaturity of neonates to handle increased bilirubin production resulting from an immaturity of the liver's excretory pathway for bilirubin at a time of its heightened production. Visible jaundice generally appears between 24-72 hours of age. Total serum bilirubin (TSB) level usually rises in full-term infants to reach a peak of 6 to 8 mg/dL by 3 days of age and then falls. A rise up to 12mg/dL is in the physiologic range. In premature infants, the peak may be 10 to 12 mg/dL on the fifth day of life, possibly rising above 15 mg/dL without any specific abnormality of bilirubin metabolism (6).

Pathological Hyperbilirubinemia:

TSB concentrations have been defined as pathological if concentration exceeds 5 mg/dl in first day of life in term neonate, 10 mg/dL on second day, or 12-13 mg/dl thereafter (7). Any TSB elevation exceeding 17 mg/dL should be presumed to be pathologic and this warrants investigation for a cause and possible intervention, such as phototherapy (8). Appearance of jaundice within the first 24 hours of life, peak TSB levels above the expected normal range, presence of clinical jaundice beyond 2 weeks in term babies and beyond 3 weeks in preterms (prolonged jaundice) and conjugated bilirubin with dark urine staining the clothes and light colored stool would be categorized under pathological jaundice. Certain factors exacerbate the jaundice in the newborn as shown in the box below.

- Polycythaemia
  - Delayed cord clamping
  - Maternofetal transfusion
  - Recipient of twin–twin transfusion
- Extravasated blood
  - Bruising (e.g. cephalhaematoma)
  - Birth trauma
  - Internal haemorrhage
- Delayed passage of meconium
- Swallowed blood
- Hypocaloric feed intake
- Dehydration
- Breastfeeding
- Prematurity

Acute Bilirubin Encephalopathy (ABE):

Bilirubin's toxicity is that of a generalised cellular poison. Disruption of membrane function, lowering of action potentials, compromise of energy metabolism and disturbance of neurotransmitter synthesis and neurotransmission are some of the mechanisms implicated (9). Advances in human genomics are identifying factors that predispose to hyperbilirubinaemia and bilirubin encephalopathy. There is evidence that bilirubin is a substrate for P-glycoprotein, a plasma membrane efflux pump found on the luminal surface of brain capillary endothelial cells and considered responsible for limiting entry of certain lipophilic substrates into the central nervous system (10). P-glycoprotein function may be inhibited by drugs. Its expression is also related to gestational maturity, and this may be a factor contributing to the greater vulnerability of the premature brain to bilirubin neurotoxicity. Also implicated is the maturational state of nerve cells exposed to bilirubin, with a greater tendency to apoptosis seen in the less well-differentiated astrocytes and neurons.

Clinically it manifests with a myriad of features. The severity is given in the form of BIND Score as shown in the table below (11).

Bilirubin Induced Neurological Dysfunction (BIND) Score (11)

Severity	Score	*Mental Status*	Date/ Time	Date/ Time	Date/ Time
None	0	Normal			
Mild	1	Sleepy, poor feeding			
Moderate	2	Lethargic, Irritable			
Severe	3	Semicoma, Seizures Coma			
Severity	Score	*Muscle Tone*			
None	0	Normal			
Mild	1	Neck Stiffness, Mild hyper-/hypotonia			
Moderate	2	Arching neck, retrocolis, Arching trunk			
Severe	3	Bowing of trunk Opisthotonus			
Severity	*Score*	*Cry pattern*			
None	0	Normal			
Mild	1	High pitched			
Moderate	2	Shrill			
Severe	3	Inconsolable			
Total Bind Score					
Nurse/MD signature					

Score of 7 to 9: Represent **severe acute bilirubin encephalopathy**; urgent interventions are recommended to minimize further **irreversible** brain injury.

Scores of 4 to 6: Represent **moderate acute bilirubin encephalopathy** and is likely to be **reversible** with urgent bilirubin reduction.

Scores of 1 to 3: Represent **mild acute bilirubin encephalopathy** and are usually **reversible** with urgent bilirubin reduction strategies.

Chronic Bilirubin Encephalopathy (Kernicterus):

Kernicterus is the name given to the characteristic pattern of yellow staining of parts of the brainstem, hippocampus, cerebellum and certain brainstem nuclei (particularly the globus pallidus and subthalamic nucleus) due to chronic bilirubin encephalopathy. The clinical manifestations of chronic bilirubin encephalopathy arise from the susceptibility to damage of the basal ganglia, brainstem auditory pathways and oculomotor nuclei (12). This anatomical preference for bilirubin deposition and vulnerability to toxicity has not been fully explained, but may be a consequence of increased blood flow and metabolic activity in these areas. Regional variation in bilirubin influx, detoxification and clearance and the variance in neuronal cell inflammatory response are also likely to be implicated.

The long-term features of bilirubin encephalopathy include extrapyramidal disturbances, auditory impairment and upward-gaze palsies and dental enamel dysplasia (13). The resulting cerebral palsy typically has an element of athetosis, which can develop as early as 18 months of age or be delayed for several years. High-frequency sensorineural deafness frequently accompanies the cerebral palsy, but may evolve in isolation. Cognitive impairment can result from bilirubin encephalopathy, but is commonly absent.

Clinical Examination of Jaundice:

Kramer described that the dermal staining of bilirubin in the newborns may be used as an approximate clinical guide to the level of jaundice (14). In the newborn the dermal staining progresses in a cephalo-caudal direction due to the difference in the amount of subcutaneous tissue. The neonate should be examined in broad daylight. The skin should be blanched by digital pressure and the underlying color of skin and subcutaneous tissues should be observed. A rough guide for level of dermal staining with level of bilirubin is as shown in the table below and **diagram number 3**

Kramer's guide to dermal staining with level of bilirubin (14)

Area of the body	Level of bilirubin
1.Face	4-6 mg/ dl
2.Chest, upper abdomen	6-10 mg/dl
3.Lower abdomen, thighs	10-12 mg/dl
4.Arms, legs	12-15 mg/dl
5.Palms, soles	>15 mg/dl

Newborns having yellow discoloration of the soles should have a quick laboratory confirmation for levels of TSB. Clinical assessment is not very reliable and accurate if a newborn has been receiving phototherapy as the skin is blanched and also if the baby has dark skin as it may obscure jaundice. Transcutaneous bilirubinometer can also be used for screening.

Investigations for Jaundice in the Newborn: the following investigations are suggested in a case of neonatal jaundice as shown in the table below.

Investigations for Jaundice in the Newborn

Early-onset jaundice	Prolonged jaundice
Total and conjugated serum bilirubin	Total and conjugated serum bilirubin
Blood group and Direct Coombs'	Thyroid function tests
Haematocrit and full blood count	Urine culture
Blood film and reticulocyte count	Liver function tests
Infection screen if indicated	IEM work-up
Serology for congenital infections	Chromosomal studies
Glucose-6-phosphate dehydrogenase screen	
Other red cell enzyme assays if feasible	

Treatment:

Two main modalities of treating newborns with hyperbilirubinemia are **Phototherapy and Double Volume Blood Exchange Transfusion.**

Phototherapy acts by converting insoluble unconjugated bilirubin into water soluble products which can be excreted in urine and stools (15-18).

Double Volume Blood Exchange Transfusion (DVET) helps by removing 80-85% of the circulating RBCs and reducing the bilirubin load (19, 20).

The AAP guidelines are widely followed for management of neonatal hyperbilirubinemia. The AAP guidelines classify infants as ≥ 35 weeks of gestation and < 35 weeks of gestation.

Guidelines for newborn infant ≥ 35 weeks of gestation (21):

AAP published charts for PT and Double Volume Exchange Transfusion (DVET) for newborn infants ≥ 35 weeks of gestation in 2004 are widely followed for this purpose as depicted in the **diagram number 4 and 5.**

Guidelines for newborn infant < 35 weeks of gestation (22):

For preterm infants < 35 weeks of gestation, the **Maisels charts** are widely used to decide the cut off for phototherapy and exchange transfusion as shown in the table given below.

Treatment guidelines in infants < 35 weeks of gestation (22)

Weight (g)	Phototherapy (mg/dl)	Exchange Transfusion (mg/dl)
<1000	Visible jaundice	10-12
1000-1500	7-9	12-15
1500-2000	10-12	15-18
2000-2500	13-15	18-20

The side-effects of phototherapy and exchange transfusion are as shown below.

Phototherapy	Exchange transfusion
Diarrhea	Blood-borne infections
Increased fluid loss via the skin	Vascular accidents
Temperature instability	Cardiac complications
Erythematous rashes	Biochemical disturbances
Tanning	Haematological disturbances
Bronze-baby syndrome	
Retinal damage	
Testicular damage in male babies	

Adjunctive treatments:

Phenobarbitone, Fluid Supplementation and IVIG have shown promising results in a few studies in reducing severe hyperbilirubinemia though more evidence is required in this direction.

Phenobarbitone: It induces the activity of uridine-di-phosphate glucuronyl transferase (UDPGT) enzyme and helps reducing bilirubin levels. It has been shown to be useful in a few studies (23-26).

Fluid Supplementation: Intravenous and oral fluid supplementation has been shown to be useful in severe hyperbilirubinemia due to subclinical dehydration by increasing the elimination of water soluble photo-products of bilirubin formed during phototherapy (27).

IVIG: IVIG therapy inhibits hemolytic breakdown of red blood cells by causing non-specific blockade of Fc receptors in the reticuloendothelial system and helps reducing hyperbilirubinemia due to ABO and Rh incompatability (28, 29).

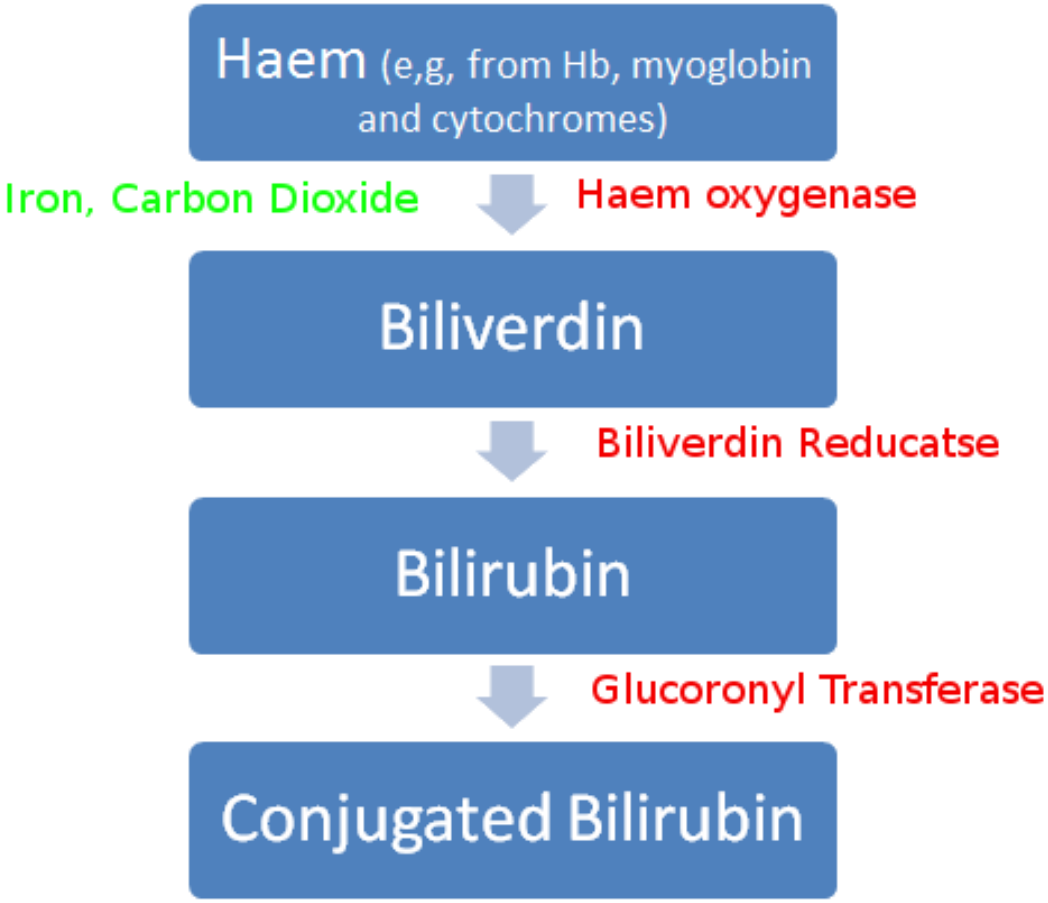
Pre-discharge Estimation of Risk for Hyperbilirubinemia (30):

Bhutani's nomogram (30) is widely used to determine the pre-discharge risk zone of hyperbilirubinemia in newborns > 35 weeks of gestation as shown below in the **diagram number 6**.

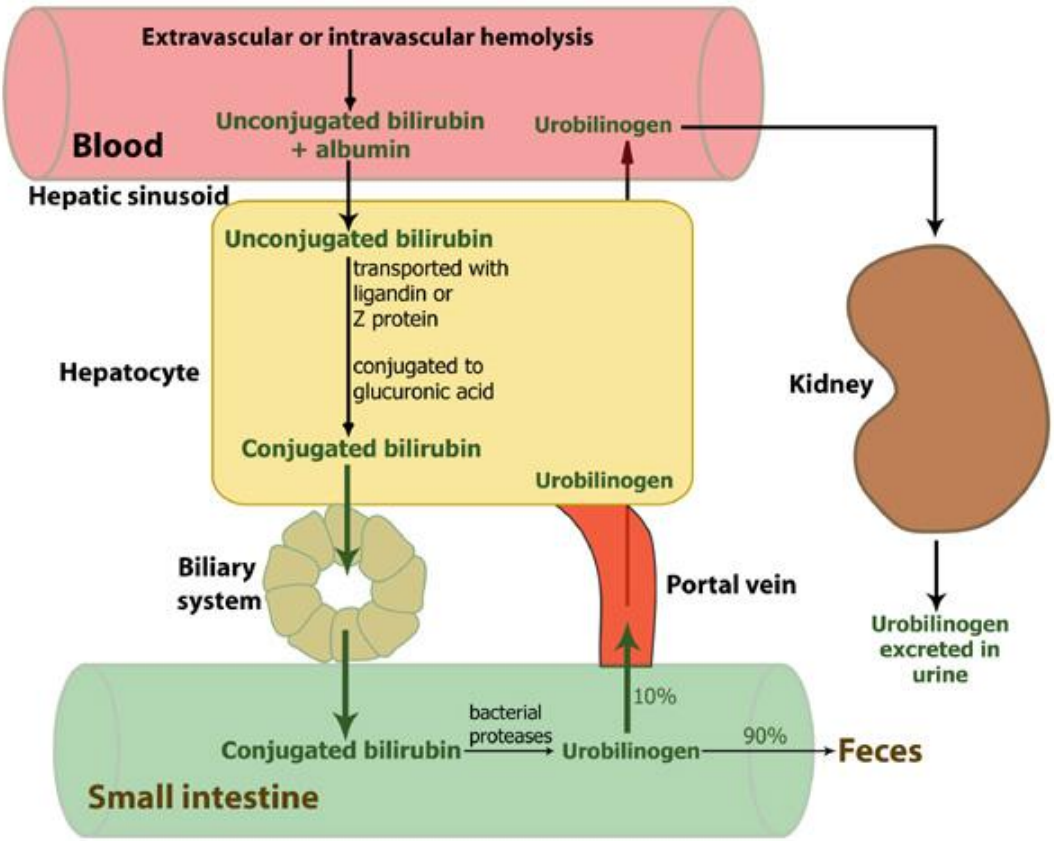
A significant proportion of neonates develop pathological hyperbilirubinemia which is defined as hyperbilirubinemia requiring treatment during the first week of life and beyond. Although the outcome for the majority is benign, infants with untreated, severe hyperbilirubinemia which is defined as serum total bilirubin level >20 mg/dL, can develop signs of acute bilirubin encephalopathy (ABE). If not treated immediately, they might go on to develop kernicterus, a chronic, very serious, neurologically devastating condition resulting from bilirubin toxicity. To prevent their occurrence prompt management of severe hyperbilirubinemia is recommended. Phototherapy is the standard treatment for such infants. Phototherapy tends to reduce bilirubin in most cases. A significant proportion of babies with severe hyperbilirubinemia may not respond to the phototherapy and may go on to require Blood Exchange Transfusion (BET), which is a highly invasive procedure with its own inherent complications. Subclinical dehydration at presentation due to evaporative losses and poor intake of breast milk could be one of main reasons for increasing the incidence and severity of jaundice in the newborns and may contribute to the failure of phototherapy. It has been

suggested that supplemental fluids in the form of increased breast feeds, formula feeds or IV fluids can reduce the risk of severe hyperbilirubinemia and the need for Blood Exchange Transfusion.

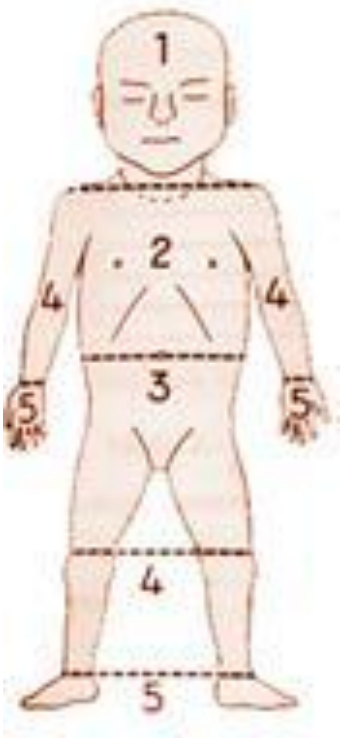
BILIRUBIN METABOLISM



BILIRUBIN TRANSPORT

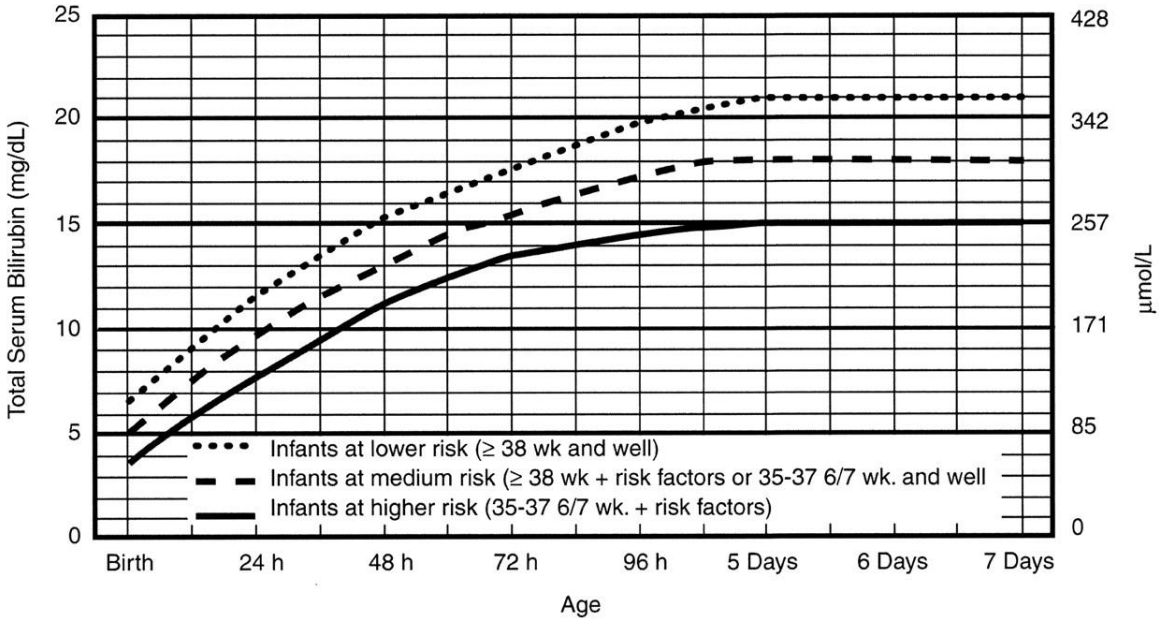


KRAMER'S GUIDE



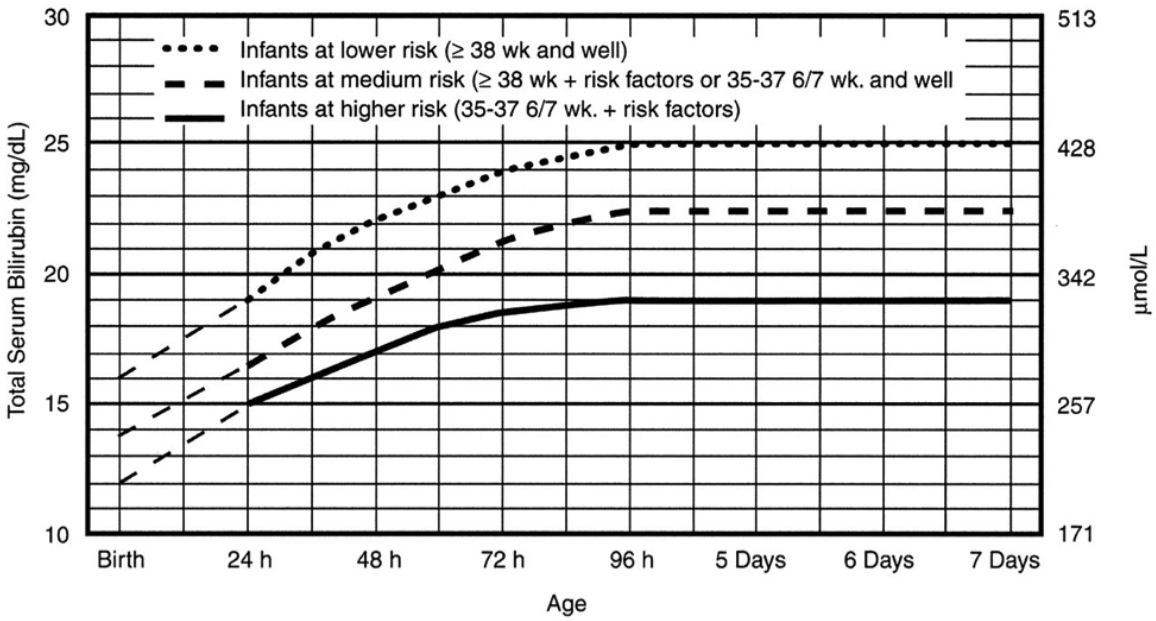
Area of the body	Level of bilirubin
1.Face	4-6 mg/ dl
2.Chest, upper abdomen	6-10 mg/dl
3.Lower abdomen, thighs	10-12 mg/dl
4.Arms, legs	12-15 mg/dl
5.Palms, soles	>15 mg/dl

AAP GUIDELINES FOR PHOTOTHERAPY FOR NEWBORNS >35 WEEKS OF GESTATION



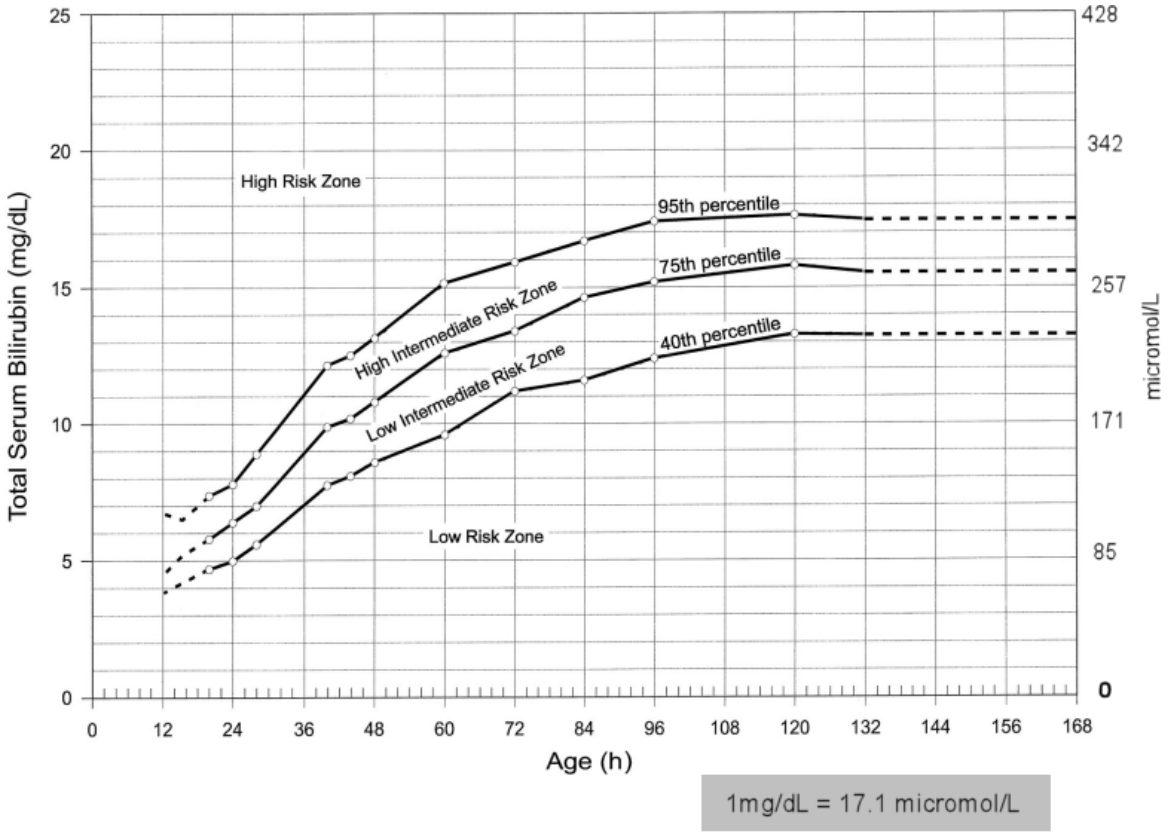
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

AAP GUIDELINES FOR EXCHANGE TRANSFUSION FOR NEWBORNS >35 WEEKS OF GESTATION



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 µmol/L) above these lines.
- Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

BHUTANI'S PREDISCHCHARGE RISK NOMOGRAM



REVIEW OF LITERATURE

Boo and Lee (31) in their study compared the rates of decline in serum bilirubin levels in severely jaundiced but healthy term infants who were given 10% of the daily maintenance fluids as either oral or intravenous fluid supplementation during phototherapy. According to them severely jaundiced healthy term infants have identical rates of decline in the unconjugated bilirubin levels during the first 4 hours of intensive phototherapy, irrespective of whether they received fluid supplementation by oral or intravenous route. They recommended that all healthy term infants with severe and significant hyperbilirubinemia requiring intensive phototherapy should be given all of their maintenance and supplemental fluid through the enteral route. They reported that the rate of decline in serum bilirubin in their newborn patients during the first 4 hours after admission was 0.6 mg/hour for the oral group and 0.65 mg/hour for the intravenous group. The American Academy of Pediatrics recommends that for intensive phototherapy to be effective, it should reduce the serum bilirubin levels by 1–2 mg/dL within 4 hours of treatment. This rate of decline in serum bilirubin in the study of Boo and Lee, which was greater than that recommended by the American Academy of Pediatrics, could be possibly explained due to more effective phototherapy lights and/or fluid supplementation. However, they also recommended that in order to detect a smaller significant difference in the rate of decline in serum bilirubin

between oral and intravenous methods of fluid supplementation, a similar study with larger sample sizes must be carried out. A limitation of their study was they did not have a control group to compare with the two methods of fluid supplementation to check out if supplementation of fluid was useful at all in the first place.

In the study done by **Iranpour et al (32)**, sixty healthy term breast-fed neonates with non-hemolytic hyperbilirubinemia were assigned randomly to receive either breast milk exclusively or intravenous fluid in addition to the breast milk during conventional phototherapy. This study showed that, the mean total serum bilirubin levels at the time of enrolment and within 84 hours after phototherapy were not statistically different between the two groups.

Mehta et al (27) conducted a randomized controlled trial of fluid supplementation in term healthy neonates with severe hyperbilirubinemia enrolling 74 newborns. They were divided into two equal groups. Group 1 (Control) received phototherapy with usual feeds. Group 2 (Extra fluid) received phototherapy with usual Feeds along with extra fluids. Extra fluids consisted of IV fluid supplementation with N/5 (0.2%) saline in 5% dextrose for a period of 8 hours during phototherapy. The volume of supplement included a presumed deficit of 50 mL/kg (equivalent to mild dehydration); half of daily maintenance requirements for an 8-hour period, which is in accordance with standard norms; and an extra 20 mL/kg/day as

allowance for phototherapy. After that babies were given 30 mL/kg/day of extra oral feeds (either expressed breast milk or formula) until phototherapy was discontinued. Phototherapy was discontinued when two TSB values obtained atleast 12 hours apart were < 15 mg/dL. Exchange transfusion was done if at 4 hours into the study TSB increased by 2 mg/dL or if at 8 hours TSB remained ≥20 mg/dL. They reported in their study that fluid supplementation in term neonates presenting with severe hyperbilirubinemia decreased the rate of exchange transfusion and duration of phototherapy. However, these authors also reported that fluid supplementation decreased the rate of exchange transfusion and duration of phototherapy more often in the patients with serum osmolality >290 mOsm/kg compared with the patients fed with breast milk only who also had serum osmolality of >290 mOsm/kg; in contrast, fluid supplementation did not decrease the rate of exchange transfusion and duration of phototherapy in the patients with serum osmolality <290 mOsm/kg significantly.

Reza Saeidi et al (33) conducted a study at Ghaem Hospital in Mashhad, Iran from October 2007 to April 2008 to evaluate the role of intravenous extra fluid therapy in accelerating the reduction of jaundice in newborns who received phototherapy. They enrolled 100 term, jaundiced neonates who had a total bilirubin of 18 mg/dl or more. The patients were randomly divided into 2 equal groups; group I (case group) was given extra

parenteral fluids besides breast feeding, and group II (control group) received only breast milk during phototherapy. The rate of bilirubin decrement, length of hospital stay, and rate of blood exchange were compared. The extra fluid was given as 1/5 normal saline in 5% dextrose at a rate of 80 cc/kg for a 2-day-old neonate, and an additional 10 cc/kg each day thereafter, to a maximum of 120 cc/kg was administered through the peripheral vein during the first 24 hours. Both groups received the same type of phototherapy, including fluorescent lamps radiating from a distance of 25 cm. They found statistically significant reduction in serum bilirubin levels in the first 24 hours. There was no significant difference in exchange transfusion rate in the two groups. They concluded that additional parenteral fluid therapy in icteric newborns can accelerate reduction in serum bilirubin levels in the first 24 hours.

In **Saini et al (34)** study, data from two previous randomized controlled trials (one published and one unpublished) of fluid supplementation in full-term neonates with severe non-hemolytic hyperbilirubinemia was used. 121 newborns with severe jaundice were given fluid supplementation in one group, and the other group received only oral feeding. They found that fluid supplementation for severe non-hemolytic hyperbilirubinemia is less likely to be beneficial in newborns delivered by caesarean/instrumental delivery compared to normal vaginal delivery.

A study was carried out in the neonatal intensive care unit of Zeynep at Kamil Maternity and Children Hospital (Istanbul, Turkey) over a period of four months by **Demirsoy et al** (35) Two hundred and fifty healthy term infants with hyperbilirubinemia were randomized to receive either solely breast milk (n=125) or both breast milk and intravenous fluid (n=125) during phototherapy. Based on the results of this study, intravenous fluid supplementation did not show any beneficial effect on the rate of decrease in serum bilirubin and decrease in duration of phototherapy treatment in healthy term infants.

Hazem A Al-Masri (36) conducted a study to evaluate the effectiveness of fluid supplementation in jaundiced healthy term infants during phototherapy. This prospective study was conducted between September 2008 and November 2009 at Prince Hashim Hospital and King Hussein Medical Centre (KHMC). A total of 80 healthy terms breast-fed and formula fed infants with hyperbilirubinemia were assigned randomly into two groups: the first group received oral feeds only (n=40) and the other group received intravenous fluid in addition to oral fed (n=40). The amount of extra fluid which was given to the supplemented group was 20% of the maintenance. There were no significant differences in the mean gestational age, the mean weight and in the mean indirect serum bilirubin level at the time of admission to the hospital between the two groups. The mean TSB levels within 72 hours after phototherapy were not statistically

different between two groups. The conclusion was that in healthy term neonates presenting with hyperbilirubinemia, there is no need to add an extra fluid during phototherapy and that by only using oral feeding the side effect of intravenous cannulation could be avoided.

Balasubramanian et al (37) conducted a study at the Post Graduate Institute of Medical Sciences, Chandigarh, to compare the incidence of hyponatremia in full-term neonates with severe hyperbilirubinemia, who received intravenous fluid supplementation with either 0.2% saline in 5% dextrose or 0.9% saline in 5% dextrose, to prevent blood exchange transfusion (BET). In this double-blind, randomized, controlled trial, full-term newborns (≥37 weeks), appropriate for gestational age, with severe non-haemolytic hyperbilirubinemia (serum bilirubin >20 mg⁄dL) were enrolled. Eligible neonates were randomized to receive either 0.2% saline in 5% dextrose (hypotonic fluid group) or 0.9% saline in 5% dextrose (isotonic fluid group) over 8 hrs, in addition to standard phototherapy. The amount of fluid supplementation given was the same as given in the study by Mehta et al. The decision to stop phototherapy or to treat with BET was based on the clinical practice guidelines given by American Academy of Pediatrics (AAP) for the treatment of neonatal hyperbilirubinemia. When STB was below the phototherapy zone, phototherapy was discontinued and rebound value was checked after 12 h. BET was done if, after 4 hours of fluid supplementation, STB increased by 2 mg/dL from baseline, or if, at 8

hours of fluid supplementation or subsequently at any time, TSB was still in the exchange zone. The primary outcome was the number of neonates developing hyponatremia (serum Na <135 mmol/L) after 8 hours. The secondary outcome variables were the duration of phototherapy, number of babies requiring BET, number of babies developing hypernatremia (serum Na >145 mmol/L) and the rate of change in serum sodium and TSB. Forty-two neonates were enrolled and analyzed in each group. Percentage of neonates developing hyponatremia after 8 hours was higher in hypotonic fluid group as compared to isotonic fluid group (48.8% vs. 10.5%, p <0.001). Nevertheless, a larger percentage in isotonic fluid group developed hypernatremia (39.5% vs. 12.2%, p <0.001). The rate of BET was similar in both groups. They concluded that in full-term neonates with severe hyperbilirubinemia, administration of hypotonic fluid to prevent BET was associated with a higher incidence of hyponatremia whereas isotonic fluid was associated with an increased incidence of hypernatremia. Based on a study by Aperia et al and by post hoc analysis they suggested that N/3 (0.3%) saline in 5% dextrose might have the least risk of hyponatremia as well as hypernatremia as a fluid of choice for fluid supplementation.

JUSTIFICATION OF STUDY

Owing to the conflicting reports found in the literature regarding the use of fluid supplementation in neonates with severe hyperbilirubinemia in preventing BET and reducing the duration of phototherapy and based on the suggestion that N/3 (0.3%) saline in 5% dextrose as supplementary fluid might have the least risk of hyponatremia as well as hypernatremia, the present study was planned and executed.

HYPOTHESIS

N/3 (0.3%) saline in 5% dextrose is useful as supplemental fluid therapy in term/AGA babies with high levels of non-haemolytic hyperbilirubinemia and subclinical dehydration in preventing BET without causing Hypo/Hypernatremia.

AIMS AND OBJECTIVES

To compare the efficacy of supplemental fluid therapy in term/AGA babies with high levels of non-haemolytic hyperbilirubinemia with N/3 saline in 5% dextrose versus control in preventing blood exchange transfusion (BET).

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OUTCOME OF THE STUDY

Primary Outcome:

To evaluate the proportion of term neonates with severe hyperbilirubinemia requiring Blood Exchange Transfusion (BET).

Secondary outcomes:

- Duration of phototherapy (PT)
- Percentage drop in TSB at 4, 8 and 24 hours of the study
- Proportion of neonates developing hyponatremia (serum Na <135 mmol/L) or hypernatremia (serum Na >145 mmol/L) at the end of 8 hours and 24 hours of IV fluid supplementation.

METHODOLOGY

Study Centres:

Department of Neonatology, Institute of Child Health (extramural unit) and Institute of Obstetrics and Gynaecology (intramural unit) of Madras Medical College, Chennai, Tamilnadu, India.

Duration of the Study:

April 2012 to March 2013

Study Design:

Prospective randomized controlled trial

Materials & Methods:

Subjects:

Neonates with severe hyperbilirubinemia with serum bilirubin >20mgs/dL admitted to the newborn wards of the Institute of Child Health and Institute of Obstetrics & Gynecology Egmore, tertiary care hospitals in Chennai, India.

Inclusion Criteria:

Term (≥37 weeks gestation)/AGA neonates presenting with severe non-hemolytic hyperbilirubinemia (total serum bilirubin [TSB] >20 mg/dL and ≤25mg/dL

Exclusion Criteria:

1. Infants with TSB >25mg/dL (427 mmol/L)
2. Acute bilirubin encephalopathy (kernicterus)
3. Evidence of hemolysis (Coombs test positive, peripheral blood smear demonstrating evidence of hemolysis or reticulocyte count was >6%)
4. Obvious signs of dehydration (i.e., sunken fontanel, reduced skin turgor, dry mucosa, tachycardia, delayed capillary refill, excessive weight loss)
5. Major congenital malformations
6. Infants already receiving intravenous (IV) fluids for any reason

Sample Size:

A pilot study carried out at the Institute of Child Health in 16 babies with severe hyperbilirubinemia (serum bilirubin >20 mg/dL and ≤25mg/dL) with 7 babies in the interventional group and 9 babies in the control group. 1 baby in the interventional group (14%) and 6 babies in the control group (66%) required blood exchange transfusion by the predefined criteria

which amounted to a difference of more than 50%. To detect a 50% difference in the need for exchange transfusion with 95% confidence ($\alpha = 0.05$) and 80% power ($\beta = 0.2$), 84 infants (42 in each group) were needed. Hence 84 infants were enrolled in the study after randomization.

Randomization:

Permuted block randomization with varying block sizes

Procedure/Intervention:

The study group (i.e., the extra fluids group) was given IV fluid supplementation with N/3 saline in 5% dextrose for a period of 8 hours along with LED phototherapy with an irradiance of around 30µw/cm^2/nm as prescribed by the AAP guidelines on phototherapy. The volume of supplement included an assumed deficit of 50 mL/kg (which is equivalent to mild dehydration); half of daily maintenance requirements for an 8-hour period, which is in accordance with standard norms; and an extra 20 mL/kg/day was given as a phototherapy allowance. In addition, the infant was allowed breast feeds at libitum. At the end of the 8-hour period, IV fluids were discontinued. Subsequently, the infant was continued on breast feeds at libitum along with the phototherapy until two subsequent bilirubin values that were obtained atleast 12 apart were less than the phototherapy cutoff. This was the point at which phototherapy was discontinued. The control group received LED phototherapy and breast feeds at libitum as was given before the randomization procedure.

Data collection and Monitoring:

Body weights, hydration status, feeding details, of the enrolled neonates were recorded at baseline. Samples for serum sodium, STB, haematocrit and reticulocyte count were also collected at enrollment. Serum sodium and STB were measured again after 8 hours of IV fluid supplementation and phototherapy in the interventional group or phototherapy alone in the control group and again at 24 hours. STB was again measured at 12 hours and thereafter every 12 hours till the baby continued to be under phototherapy. A rebound STB value was also checked 12 hours after discontinuation of phototherapy. Neonates were evaluated daily for body weight, hydration status, feeding details, fluids intake, urine output, stool frequency and clinical signs of bilirubin encephalopathy. The infants were closely monitored till discharge from the hospital. Serum sodium was measured by ion-selective electrode method by means of Auto-analyzer. Bilirubin was estimated in the lab by diazo method and the values were obtained within an hour. The irradiance was measured periodically by a standard fluxmeter and kept above 30µwatt/cm^2/nm. The decision to either stop phototherapy or to treat with BET was based on the clinical practice guidelines given by American Academy of Pediatrics (AAP) for the treatment of neonatal hyperbilirubinemia. When two STB values were below the phototherapy zone, phototherapy was discontinued and rebound value was checked after 12 h. BET was done if, after 4 h of fluid

supplementation, TSB increased by 2 mg/dL from baseline, or if, at 8 hours of fluid supplementation or subsequently at any time thereafter, while under phototherapy, TSB was still in the exchange zone.

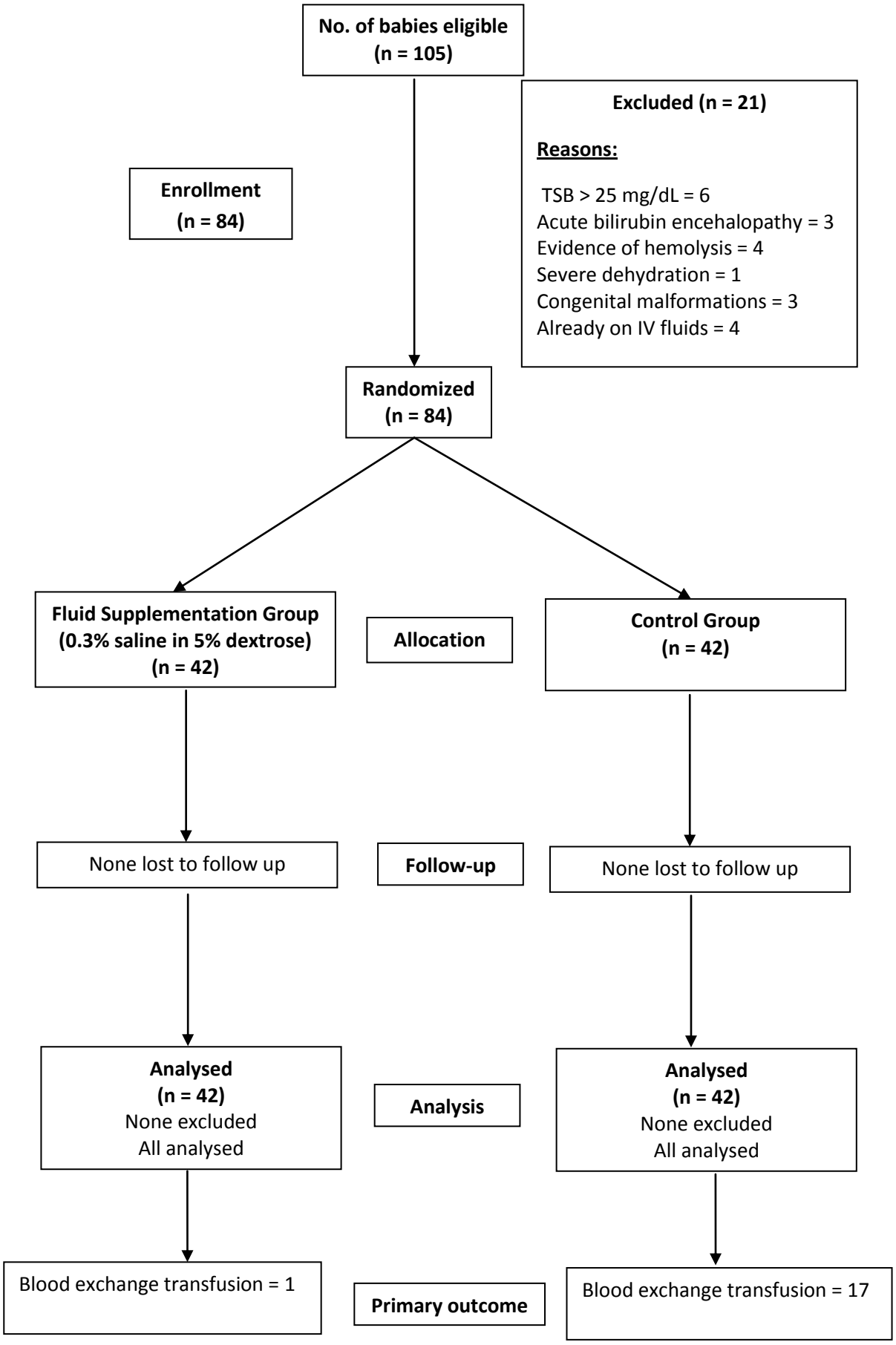
Data Collection Proforma:

Data was collected in prescribed proforma given in the annexure.

Statistical Analysis:

All statistical analysis was performed according to intention to treat principle by SPSS software version 18 for Windows (SPSS Inc., Chicago, IL, USA). Standard statistical tests were employed. Categorical variables were analyzed with chi square test and continuous variables were analyzed using student's t test. Non parametric tests were used if the variables were found to be skewed in distribution. Statistical significance was considered at a p value of <0.05.

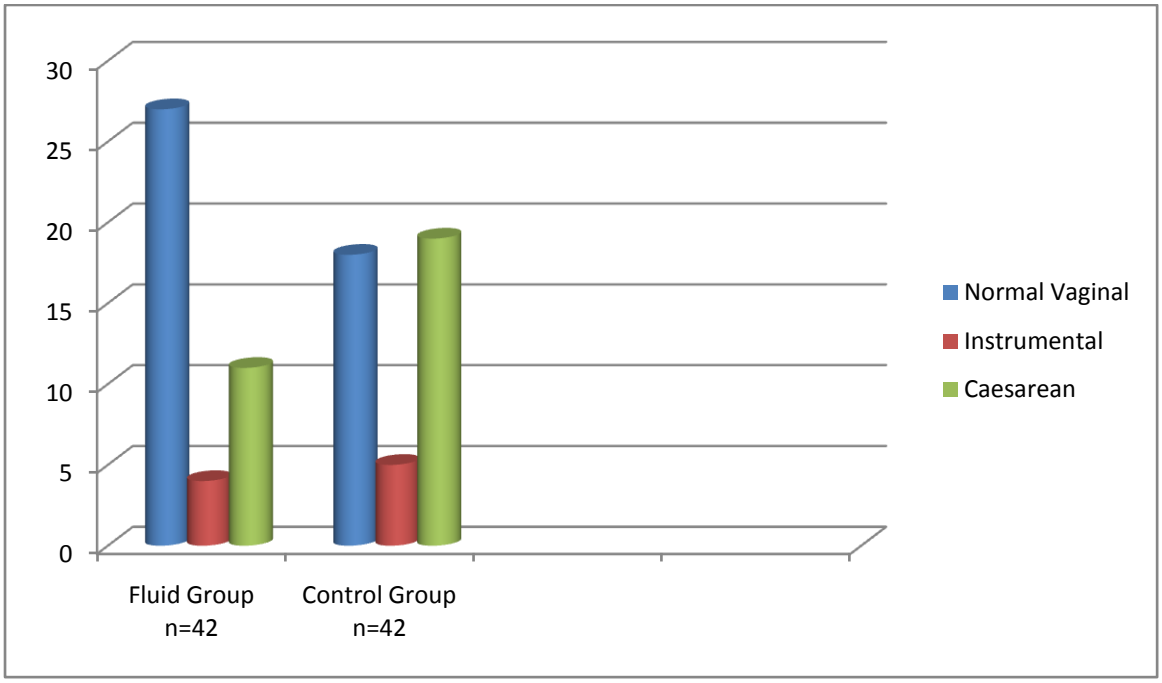
FLOW OF PATIENTS IN THE STUDY (CONSORT DIAGRAM)



TABLES

Table 1-Baseline Neonatal Demographic Parameters			
Characteristic	**Fluid Supplementation Group n = 42**	**Control Group n = 42**	**P Value**
Extramural unit (%)	23 (54.8)	25 (59.5)	0.659
Intramural unit (%)	19 (45.2)	17 (40.5)	0.659
Gestational age (weeks)	38.7 ± 0.8	39 ± 0.8	0.214
Males (%)	21 (50)	22 (52.4)	0.827
Females (%)	21 (50)	20 (47.6)	0.827
Birth weight (g)	2922 ± 380	2886 ± 331	0.645
Percent weight loss	5.7 ± 2.8	5.8 ± 2.5	0.924
Normal vaginal delivery (%)	27 (64.3)	18 (42.8)	0.110
Instrumental delivery (%)	4 (9.5)	5 (12)	0.110
Caesarean section (%)	11 (26.2)	19 (45.2)	0.110
Onset of jaundice (day)	3.0 ± 0.8	2.8 ± 0.8	0.507
Age at inclusion (day)	4.4 ± 1.5	4.3 ± 1.4	0.675

The neonatal demographic variables that could affect TSB were distributed evenly between the fluid supplementation group and the control group. (Table 1)



MODE OF DELIVERY IN THE TWO GROUPS

Table 2-Baseline Neonatal Laboratory Parameters			
Characteristic	**Fluid Supplementation Group n = 42**	**Control Group n = 42**	**P Value**
TSB at enrolment (mg/dL)	22 ± 1.7	22 ± 1.8	0.884
Reticulocyte count (%)	2.1 ± 0.7	2.1 ± 0.8	0.999
Haematocrit (%)	46.3 ± 3.5	46.5 ± 3.5	0.786
Serum sodium (mmol/L)	141.7 ± 3.8	143.8 ± 4.8	0.266

The neonatal laboratory variables that could affect TSB were also distributed evenly between the fluid supplementation group and the control group. (Table 2)

Table 3-Baseline Maternal Parameters			
Characteristic	**Fluid Supplementation Group n = 42**	**Control Group n = 42**	**P Value**
Maternal age	23.4 ± 3	24.6 ± 2.3	0.190
Maternal hypertension (%)	2 (4.8)	2 (4.8)	1.000
Maternal diabetes (%)	1 (2.4)	0 (0)	0.999
Primigravida	29 (69)	25 (59.5)	0.669
Second gravida	10 (23.8)	12 (28.6)	0.669
Third gravida	3 (7.2)	5 (11.9)	0.669
Primipara	30 (71.4)	27 (64.3)	0.758
Second para	10 (23.8)	12 (28.6)	0.758
Third para	2 (4.8)	3 (7.1)	0.758
First livebirth	30 (71.4)	27 (64.3)	0.643
Second livebirth	11 (26.2)	12 (28.6)	0.643
Third livebirth	1 (2.4)	3 (7.1)	0.643

The maternal demographic variables that could affect TSB were also distributed evenly between the fluid supplementation group and the control group. (Table 3)

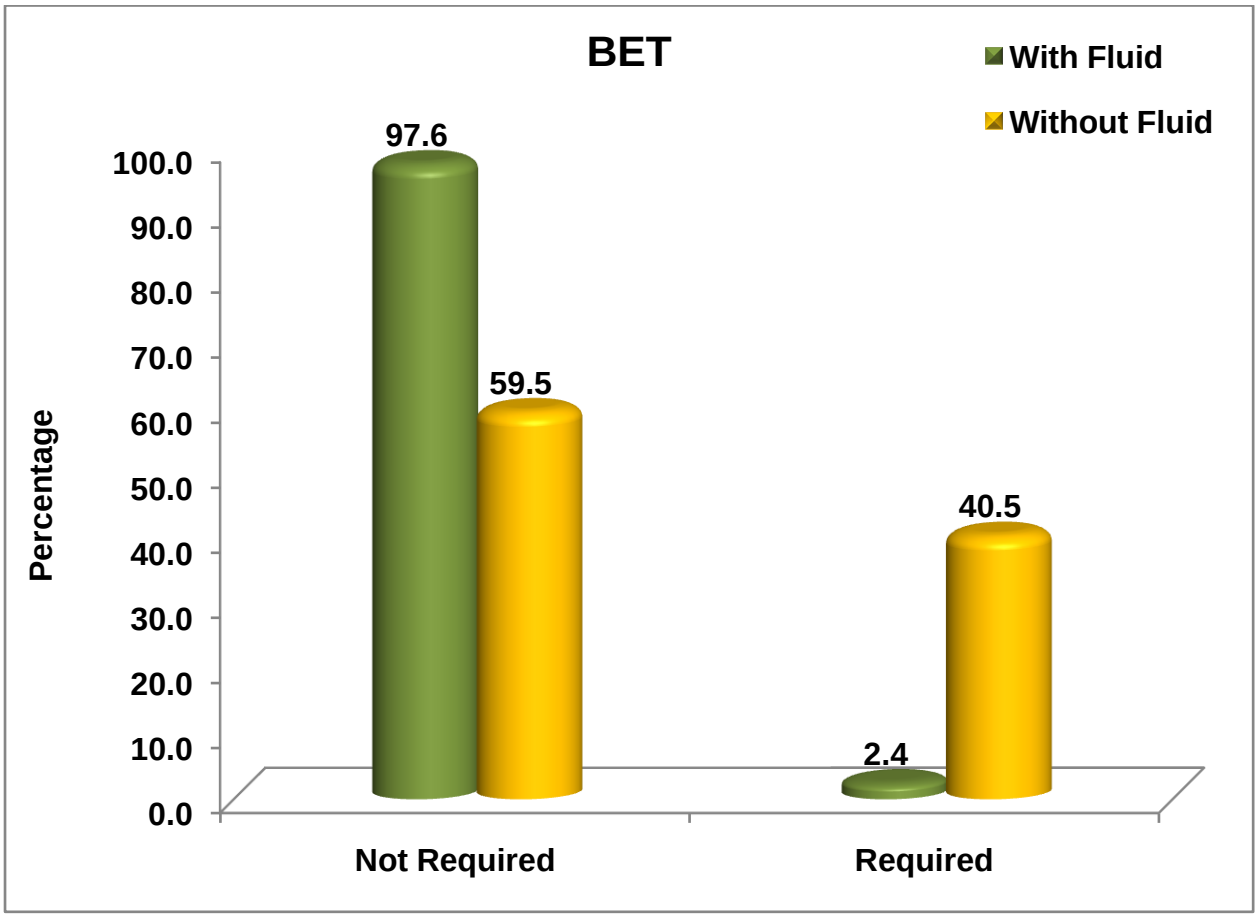
Table 4-Primary Outcome			
Characteristic	**Fluid Supplementation Group n = 42**	**Control Group n = 42**	**P Value**
Blood exchange transfusion (%)	1 (2.4)	17 (40.5)	0.001

Significantly fewer infants in the fluid supplementation group than in the control group (1 [2.4%] vs 17 [40.5%] (p = 0.001); underwent exchange transfusion. (Table 4)

Table 5-Primary Outcome Relative Risk and 95% CI (Inferential Statistics)			
Characteristic	**Relative risk**	**95% CI**	**P Value**
Blood exchange transfusion	0.06	0.01-0.42	0.002

The relative risk = 0.06; 95% CI = 0.01 to 0.42 (p = 0.002) (Table 5)

BLOOD EXCHANGE TRANSFUSION (BET) REQUIRED PERCENTAGES BETWEEN THE TWO GROUPS



KAPLAN MEIER CURVES SHOWING THE PROBABILITY OF BLOOD EXCHANGE TRANSFUSION IN THE TWO GROUPS

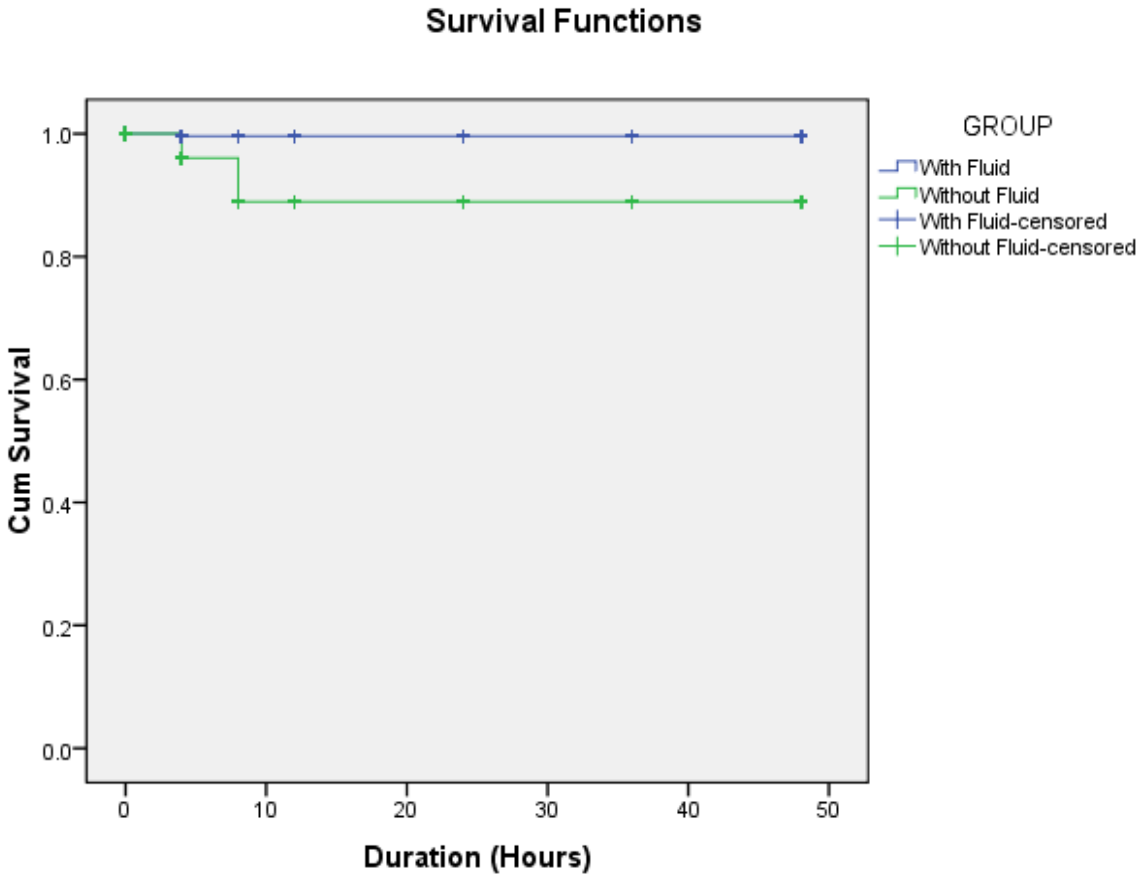


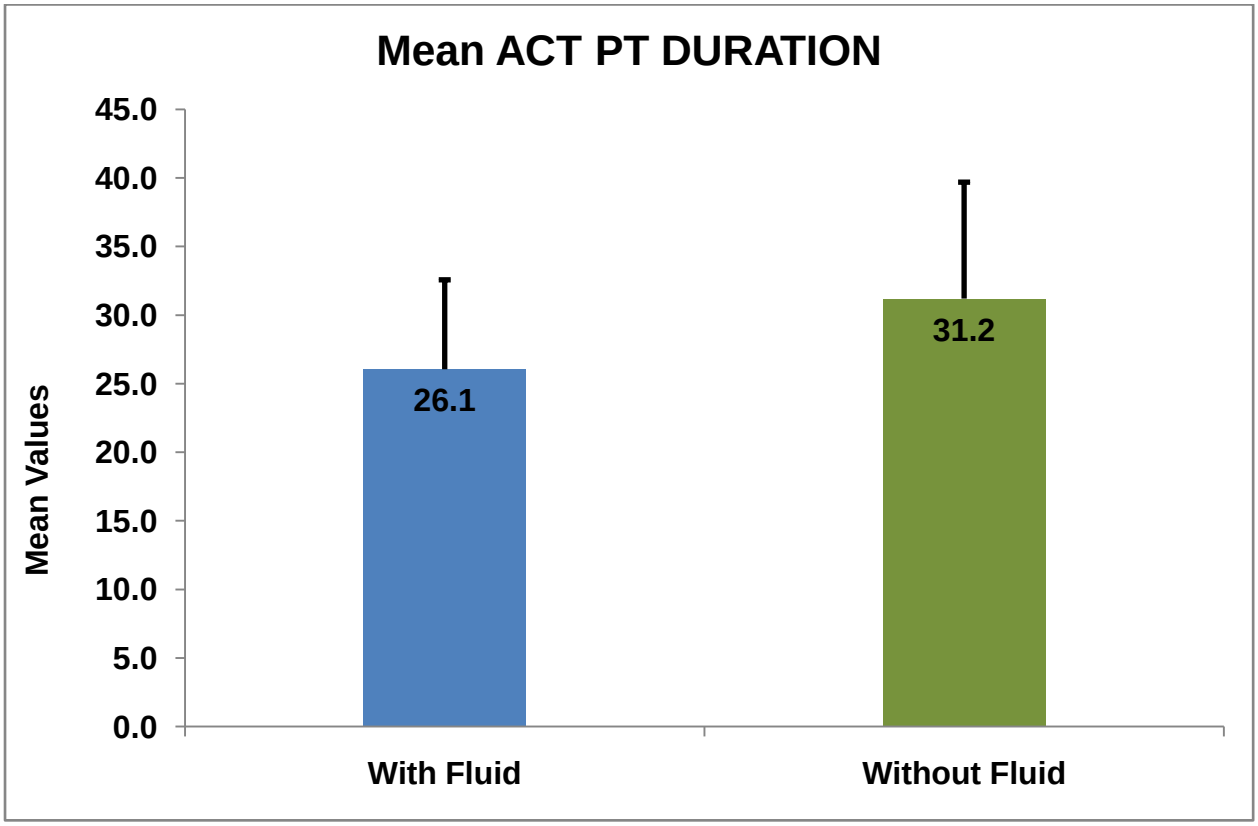
Table 6-Secondary outcome			
Characteristic	**Fluid Supplementation Group n = 41**	**Control Group n = 25**	**P Value**
Phototherapy duration excluding BET in hours (Mean ± SD)	26.1 ± 6.5	31.2 ± 8.4	0.013

The mean duration of phototherapy after inclusion in the study was 5.1 hours shorter in the fluid supplementation group (26 ± 6.5 hours vs 31 ± 8.4 hours; p = 0.013) (Table 6).

The irradiance of phototherapy units was similar in the 2 groups ($\geq$30$\mu W/cm^2/nm$).

Both the groups were on exclusive breast feeding during the entire period of phototherapy.

MEAN DURATION OF PHOTOTHERAPY BETWEEN THE TWO GROUPS



KAPLAN MEIER CURVES SHOWING THE PROBABILITY OF REMAINING UNDER PHOTOTHERAPY IN THE TWO GROUPS

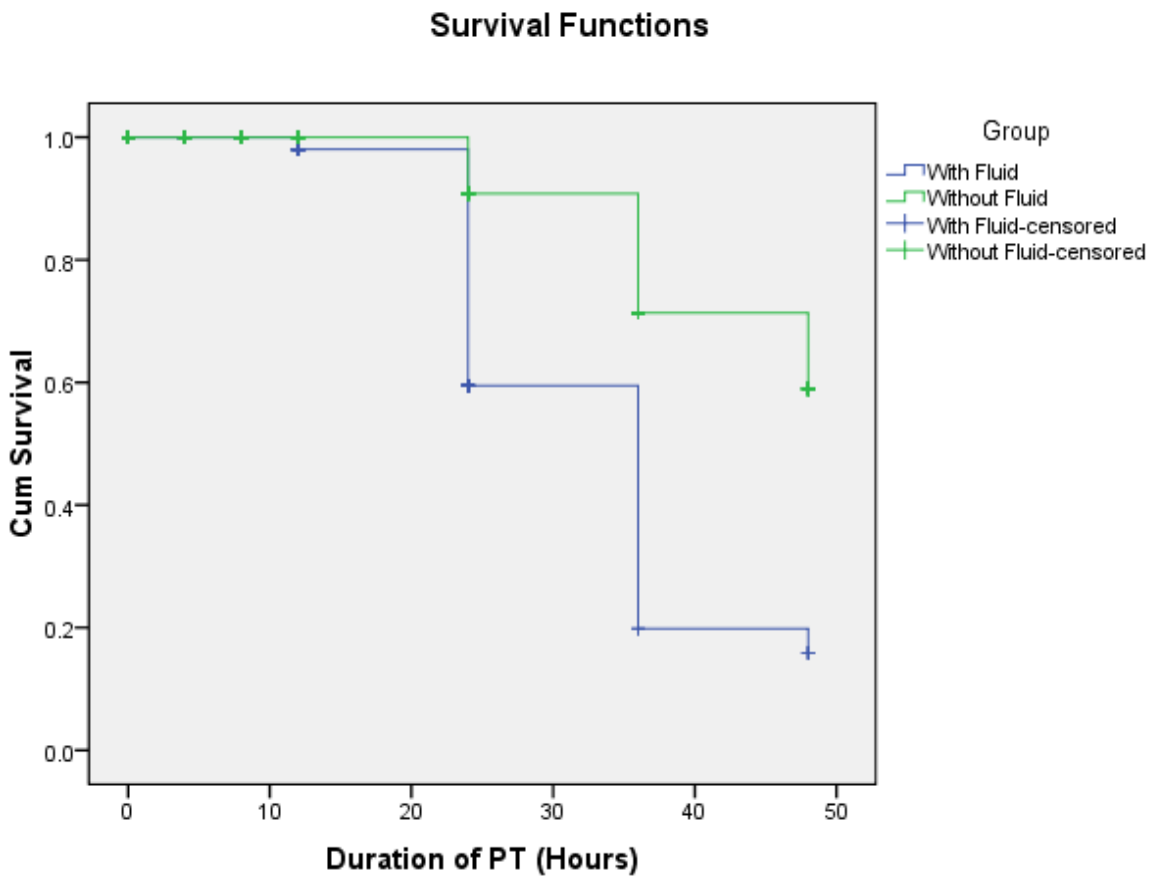


Table 7-Total Serum Bilirubin (TSB) Trends							
Hours of Study	**Fluid Supplementation Group**			**Control Group**			**P value**
	n	**TSB in mg/dL**	**Percent (%) Fall in TSB**	**n**	**TSB in mg/dL**	**Percent (%) Fall in TSB**	
At inclusion	42	22 ± 1.7	-	42	22 ± 1.8	-	0.884
4 hours	41	19.3 ± 2.0	12.4 ± 5.4	35	21.3 ± 2.6	6.0 ± 3.9	0.001
8 hours	41	17.4 ± 1.4	20.1 ± 6.1	25	19.9 ± 3.3	14.4 ± 5.1	0.001
24 hours	41	13.6 ± 1.6	37.4 ± 8.2	25	14.0 ± 1.6	33.5 ± 6.6	0.049

The number of babies at 4, 8 and 24 hours is less than that at inclusion because it excludes TSB data of babies who underwent exchange transfusion before that time.

$$\text{*Percent (\%) fall in TSB} = \frac{\text{TSB at inclusion - TSB at specific time}}{\text{TSB at inclusion}} \times 100$$

TSB levels were similar in the 2 groups at inclusion but were significantly lower at 4 and 8 hours in the fluid supplementation group. The percentage drop in TSB at 4, 8, and 24 hours of study was also significantly greater in the fluid supplementation group. (Table 7)

TRENDS IN TOTAL SERUM BILIRUBIN (TSB) IN THE TWO GROUPS

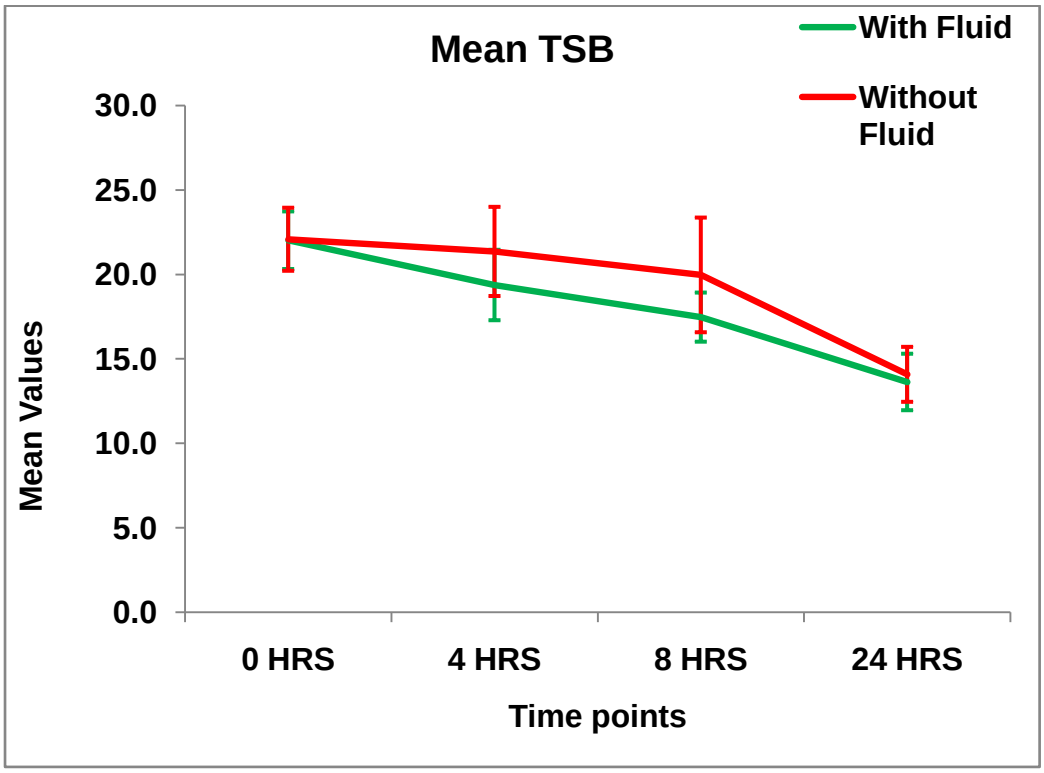


Table 8-Secondary Outcome			
Characteristic	**Fluid Supplementation Group n = 42**	**Control Group n = 42**	**P Value**
Serum sodium at inclusion (Mean ± SD)	141.7 ± 3.8	143.8 ± 4.8	0.266
Serum sodium at 8 hours (Mean ± SD)	143.8 ± 3.3	143.5 ± 4.6	0.767
Serum sodium at 24 hours (Mean ± SD)	141.7 ± 2.7	142.2 ± 3.1	0.419

Serum sodium at 0, 8 and 24 hours was similar in both the groups and no significant disturbances in sodium homeostasis (hyponatremia or hypernatremia) occurred in either fluid supplementation group or control group. (Table 8)

TRENDS IN SERUM SODIUM IN THE TWO GROUPS

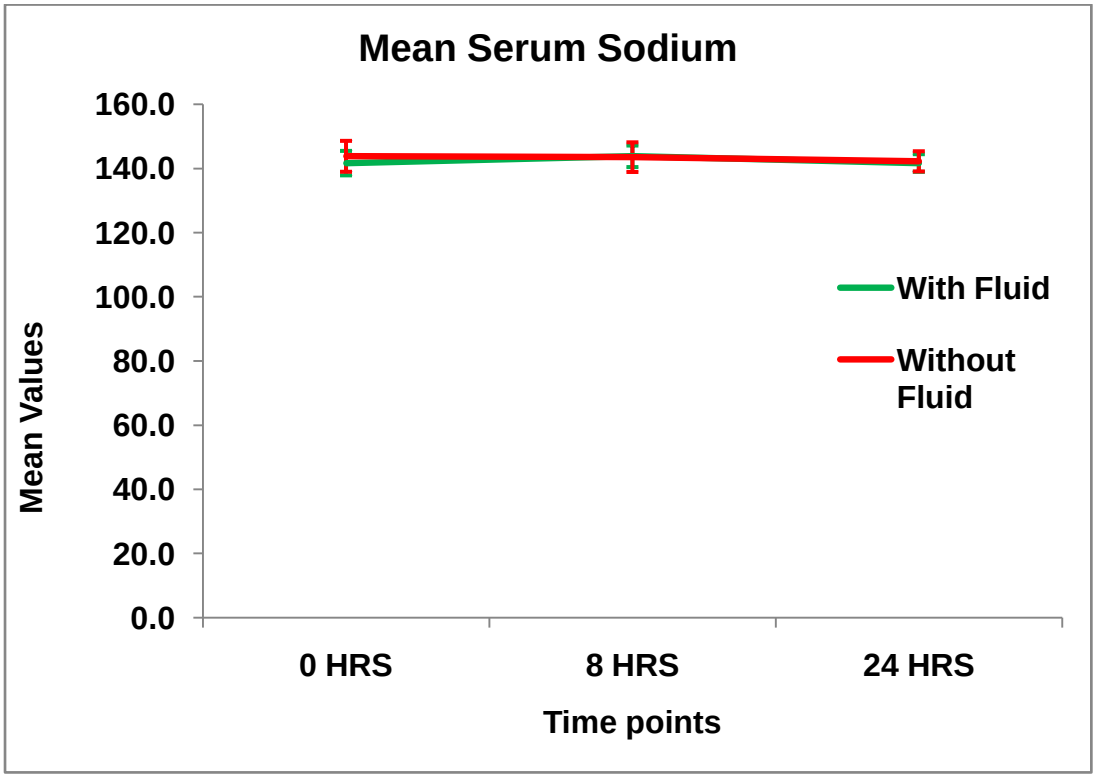


Table 9-Complications		
Complication	Fluid Supplementation Group	Control Group
Bilirubin encephalopathy	None	None
Dehydration	None	None
Over hydration	None	None
Thrombophlebitis	None	None
Sepsis	None	none

None of the infants in either of the groups developed features of bilirubin encephalopathy, any subsequent episodes of dehydration or over hydration, serious thrombophlebitis, or evidence of sepsis. (Table 9)

DISCUSSION

In our study infants with serum bilirubin of >20 and ≤25 mg/dL were chosen for study as in accordance with the American Academy of Pediatrics (AAP) guidelines for managing hyperbilirubinemia in newborns >35 weeks gestation, exchange transfusion is usually done at TSB >25 mg/dL (427 mmol/L). Exchange transfusion carries a mortality rate of approximately 3 in 1000 procedures. Significant morbidity in the form of apnea, bradycardia, cyanosis, vasospasm, thrombosis, necrotizing enterocolitis occurs in as many as 5% of BETs, the risk of mortality is 0.3% and the risks associated with the use of blood products must always be taken into consideration. Incidence of complications may be higher in developing countries. Phototherapy units, although simple, are also expensive and difficult to maintain. Phototherapy for long hours also has its own attendant complications. If providing fluid supplementation decreases the need for exchange transfusion and reduces the need for phototherapy without undue risks, then it should be cost effective and must be considered.

In our study appropriate for gestation term neonates with non hemolytic hyperbilirubinemia were enrolled following permuted block randomization, generated by computer software, to evenly match the

groups and to negate the effect of potential confounding factors. Blinding could not be done in this randomized controlled trial; however, the laboratory personnel performing the TSB and other biochemical investigations were sent coded samples and were unaware of the group allocation. The study design was able to ensure matching of demographic variables and other factors that could affect the subsequent TSB levels.

According to the AAP recommendations, a weight loss of >12% is an indicator of significant dehydration (21). Mild dehydration may be subtle and may not produce prominent clinical signs; therefore, weight loss and other clinical signs may not manifest sufficiently enough to make a diagnosis of mild dehydration. Serum osmolality of >290 mosm/kg could give an indication but unfortunately it could not be done in the present study. Serum sodium was done which could act as a surrogate marker of subclinical dehydration. The fact that in our study neonates with severe hyperbilirubinemia were either normonatremic or hypernatremic and none hyponatremic probably stresses the same. In our study the volume of calculated fluid deficit along with half of the maintenance requirements and the phototherapy requirements was given by the IV route rather than oral route, because the effectiveness of oral rehydration, though good enough, may not be sufficiently reliable and quick in the setting of severe hyperbilirubinemia. One of the contemplated mechanisms by which fluid

supplementation could have helped is expansion of intravascular volume, leading to **dilutional** lowering of TSB. The more important effect would be enhanced **renal**, **biliary** and **bowel functions**. This is because the photo products of bilirubin formed during phototherapy are eliminated in the urine and stools. Breast feeds at libitum that accompanied and followed the initial IV fluid supplementation possibly helped by decreasing enterophepatic circulation and thereby interrupting the reabsorption of bilirubin from the gut. We did not give any formula feeds to both the groups based on our unit policy and also because we did not want to interrupt the mother child bonding. It has been suggested of late that breast-fed infants can autoregulate and increase milk intake and decrease the insensible water loss as well while receiving phototherapy; however, it may not always be true. It is possible that the breast milk output may not increase or the feeding may not get augmented because infants when exposed to phototherapy tend to become more sleepy than usual. This would suggest that we cannot satisfactorily rely on the infants' own auto-regulatory mechanisms to augment the intake of breast milk in the presence of severe hyperbilirubinemia. IV site complications can be minimized by strict adherence to asepsis and proper care. None of these were observed in our study.

The incidence of BET and the duration of phototherapy along with the percentage drop in TSB at 0, 4, 8 and 24 hours were significantly less

reaching statistical significance in the fluid supplementation group than the control group which is in concordance with the earlier studies. Perhaps the effect was complemented in our study by the use of blue light LED phototherapy with an irradiance of atleast 30µwatts/cm^2/nm (38).

The IV fluid chosen for supplementation was N/3 saline in 5% dextrose (Fresinius Kabi) based on the suggestion of earlier study by Balasubramanian et al (37) which was further based on the suggestion by Aperia et al. In our study no statistically significant difference in sodium homeostasis occurred though in the study by Balasuramanian et al (37) the use of N/5 saline in 5% dextrose (hypotonic saline) resulted in hyponatremia and use of NS in 5% dextrose (isotonic saline) resulted in hypernatremia. Perhaps the use of N/3 saline in 5% dextrose maintained the normal sodium balance. The serum sodium at 0, 8 and 24 hours was not statistically different between the two groups.

Hansen (39) reported in their study 4 infants with serum bilirubin levels ranging from 32.1 to 36.3 mg/dL in whom phototherapy decreased TSB by >10 mg/dL in 2 to 5 hours. However, of these 4 infants, 3 were clinically dehydrated, 2 received IV fluids, and all received oral supplements. These findings lend support to the role of rehydration and decreasing enterophepatic circulation in audmenting the effects of phototherapy. The fluid supplementation given in our study was mainly for mild dehydration which could be subclinical in presentation. Mothers were encouraged to

breast feed more often to interrupt enterophepatic circulation naturally. The strategy was successful in significantly reducing the need for blood exchange transfusion and reducing the duration of phototherapy.

The trial by **Boo and Lee (31)** compared IV and oral fluid supplementation. They reported severely jaundiced healthy term infants had similar rates of decrease in TSB levels during the first 4 hours of intensive phototherapy, irrespective of whether they received oral or intravenous fluid supplementation. But they did not have a control group to determine whether fluid supplementation itself played any role. The study included infants with clinical dehydration as well as no dehydration, and actual fluid intakes were not reported. In our study we chose to give IV fluid supplementation along with feeds at libitum to avoid the uncertainty of oral feeding as we were dealing with severe hyperbilirubinemia in term neonates which could be detrimental if not managed promptly.

In the study done by **Iranpour (32)**, sixty healthy breast-fed neonates with non-hemolytic hyperbilirubinemia were assigned randomly to receive either breast milk exclusively or intravenous fluid in addition to breast milk during conventional phototherapy. Neonates in the fluid-supplemented group received an additional 25% of their maintenance fluid requirement. They showed that, the mean total serum bilirubin levels at the time of enrollment and within 84 hours after phototherapy were not statistically different between two groups. This was probably because the

IV supplementary fluid given by them was only 25% and that too over an extended period of 24 hours. This fluid supplementation was perhaps not sufficient to correct the mild subclinical dehydration with 5% fluid deficit in term babies with severe non-hemolytic hyperbilirubinemia which needs atleast 50ml/kg over a shorter span of time. Using this strategy we were able to show statistically significant reduction in the need for blood exchange transfusion and the duration of phototherapy in these infants.

In the study done by **Mehta et al (27)** which is the harbinger of our study, the study group of term neonates with severe non-hemolytic hyperbilirubinemia, (i.e., the extra fluids group) was given IV fluid supplementation with N/5 (0.2%) saline in 5% dextrose for a period of 8 hours. The volume supplemented was calculated based the following calculation-50 ml/kg for mild dehydration, 20 ml/kg for phototherapy allowance and half of the eight hours daily maintenance fluid which totaled to approximately 80ml/kg of fluid supplementation over 8 hours. In addition, the infant continued to receive feeds as were given before entry into the study. In the study group at the end of the 8-hour period, hydration status was once again reassessed and the IV fluids were discontinued. Thereafter the baby continued to receive breast or formula feeds as before and in addition was given 30 mL/kg/day of extra oral feeds (expressed breast milk or formula milk) until the time phototherapy was discontinued. The control group was continued on breast or formula feeds ad libitum as

was given prior to the randomization procedure. They showed a significant reduction in the need for blood exchange transfusion and the duration of phototherapy in the study group. This was particularly true when the serum osmolality was >290 mOsm/kg, which occurs with subclinical dehydration. However they reported higher incidence of hyponatremia with the use of 0.2% saline in 5% dextrose as fluid for supplementation as it is hypotonic. Hence in our study we chose N/3 saline in 5% dextrose based on the suggestion of subsequent studies, for fluid supplementation in the extra fluid group. The quantity of the fluid was the same as in this study. The results were similar to this study. At the same time the risk of hypo/hypernatremia was avoided by the use of N/3 (0.3%) saline in 5% dextrose.

In the study done by **Saeidi et al (33)**, wherein term neonates with severe hyperbilirubinemia in the study group were given IV fluid supplementation of atleast 80ml/kg over 24 hours, significant reduction in serum bilirubin levels in the first 24 hours was demonstrated though there was no change in the need for blood exchange transfusion. In our study we were able to show a significant reduction in the need for blood exchange transfusion as well, in addition to significant reduction in serum bilirubin and duration of phototherapy. This is perhaps because though the amount of fluid was almost similar to this study, it was given over a shorter time period of 8 hours in our study.

Saini et al (34) did a sub study based on two earlier studies of IV fluid supplementation in newborns with severe hyperbilirubinemia, one published and one unpublished. They analysed the causes for the failure of IV fluid supplementation. By multiple logistic regression model they concluded that Fluid supplementation for severe non-hemolytic hyperbilirubinemia is less likely to be successful in preventing BET in full-term neonates born by cesarean or instrumental delivery as compared to babies born by normal vaginal delivery. In our study the normal vaginal, instrumental and cesarean deliveries were evenly distributed between the extra fluid group and the control group, thus eliminating the bias due to mode of delivery.

Demirsoy et al (35) carried out a randomized controlled study on effect of IV fluid supplementation during phototherapy on breast fed term neonates with severe hyperbilirubinemia. They did not find a significant reduction in fluid supplementation group and the control group in the rate of exchange transfusion and duration of phototherapy, irrespective of the serum osmolality (>or<290 mOsm/kg). The quality and the amount of fluid given was the same as employed in the study by Mehta et al. This difference could be due to lower mean of serum osmolality levels in both study and control groups and higher exchange cut off of >25mg/dL used in this study. In our study though we did not measure the serum osmolality and we used almost the same criteria for exchange as was used by Mehta et al.

We found the results to be almost the same in our study with significant reduction in the rates of blood exchange transfusion and the duration of phototherapy in the fluid supplementation group compared to the control group.

Al-Masri (36) conducted a study to find out if it was necessary to supplement healthy term infants with fluid during phototherapy? They concluded that there was no need to add extra fluid during phototherapy, as they did not find statistically significant decline in serum bilirubin at identical time points among supplemented and the non-supplemented groups. Though the fluid used was the same as in earlier studies, the amount of extra fluid given to the supplemented group was only 20% of the maintenance. Again this was almost similar to the amount of fluid used by Iranpour et al and the results were identical in these two studies. Had higher amount of fluid been used in accordance with mild dehydration principle, the results could have been the same as observed in the study by Mehta et al and also in our study.

Balasubramanian et al (37) carried out the study with two different types of fluid for fluid supplementation in the two groups as 0.2% saline in 5% dextrose in one group (hypotonic fluid group) and 0.9% saline in 5% dextrose in the other group (isotonic fluid group) of term babies with severe hyperbilirubinemia. The fluid supplementation was carried out for 8 hours with the same amount as was used by Mehta et al in their study.

They found that the rate of blood exchange transfusion and the duration of phototherapy was the same in both the groups which was also similar to the study by Mehta et al. however they observed that Proportion of neonates developing hyponatremia after 8 hours of IV fluid supplementation was significantly higher in hypotonic fluid group as compared to isotonic fluid group (48.8% vs. 10.5%) and proportion developing hypernatremia in isotonic fluid group was also significantly higher (39.5% vs. 12.2%). Hence their inference was an ideal fluid would be of a strength which was between normal saline and 0.2% saline. Based on the study by Aperia et al. (40), a term healthy neonate of 3 kg could excrete a maximum of 12 mEq of sodium over 8 hours in urine. An ideal fluid for supplementation in such neonates could be N/3 (0.3%) saline in 5% dextrose, which would then give a sodium load of 4 mEq/kg over 8 hours (12.2 mEq for a 3 kg neonate). Based on this post hoc analysis, they suggested that N/3 (0.3%) saline in 5% dextrose might carry the least risk of hyponatremia as well as hypernatremia and hence could be the fluid of choice for fluid supplementation.

This formed the basis of our research. We were able to prove in a randomized controlled trial that IV fluid supplementation in neonates with severe non-hemolytic hyperbilirubinemia with 0.3% saline in 5% dextrose significantly reduced the risk of blood exchange transfusion and duration of phototherapy without causing disturbances in sodium homeostasis.

Though no IV site complications were observed in our study, it is a known source of nosocomial sepsis. Hence strict adherence to asepsis practices and vigilant monitoring is a must to carry out this adjunctive method of management of severe hyperbilirubinemia in newborn babies.

LIMITATIONS OF THE STUDY

1. The study was conducted with a power of 80%. A larger sample size with 90% power would add more meaningful strength to the observations in this study.
2. The oral intake could not be strictly monitored as all babies were breastfed at libitum and no extra EBM or formula feeds were used as per the baby friendly hospital initiative.
3. The serum osmolality which generally tends to become >290 mOsm/kg with subclinical dehydration, could not be measured in our study. Hence we could not do a subset analysis of whether fluid supplementation was more useful in this group of babies.
4. We did not have oral fluid supplementation limb in our study. As suggested by some studies, the possibility of supplementation of extra fluids in the form of EBM or accepted equivalent by oral route alone in babies with severe hyperbilirubinemia needs to be further explored.

CONCLUSIONS

1. The IV fluid supplementation with 0.3% saline in 5% dextrose in newborns with severe non-hemolytic hyperbilirubinemia was useful in significantly reducing the need for blood exchange transfusion. ($p = 0.001$)
2. In addition the total duration of phototherapy reduced significantly in the fluid supplementation group ($p = 0.013$)
3. More percentage drop in serum bilirubin was observed in the fluid supplementation group at 4, 8 and 24 hrs of study ($p = 0.001$, 0.001 and 0.049).
4. Moreover the use of 0.3% saline in 5% dextrose as fluid for supplementation did not lead to any significant disturbances in sodium homeostasis in the form of hyponatremia or hypernatremia at 8 and 24 hours of study, which could be detrimental to the neonates. ($p = 0.767$ and 0.419). N/3 (0.3%) saline in 5% dextrose appears to be the ideal fluid of choice for fluid supplementation in term neonates with non-hemolytic severe hyperbilirubinemia.

To conclude, this study reinforces the effectiveness of IV fluid supplementation in full term neonates with severe non-hemolytic hyperbilirubinemia in reducing the rate of blood exchange transfusion and the duration of phototherapy and further adds a new dimension regarding the usefulness of 0.3% saline in 5% dextrose as supplementary fluid of choice in maintaining the sodium homeostasis.

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PROFORMA

Patient n. _____ **Hospital** **ICH** □
Date_____ **IOG** □

Group of Randomization: **Supplemental Fluid therapy Group** □

Control Group □

Name _____Date of birth _____

Gender:_____Time of birth _____

Obstetric history:

Maternal age___G_P_L_A_Previous pregnancies, n. __Previous deliveries, n. __

Antenatal history:

Maternal hypertension/Preeclampsia, (yes/no) _____ Diabetes, (yes/no) _____

Placenta abruptio, (yes/no) __ Maternal anemia, (yes/no)____Other, (specify)__

Amniotic fluid: Clear □ Meconium stained □ Other, (specify)_____

Mode of delivery: Vaginal □ _____Caesarean section □ (reason): _____

Gestational age (wks)_____Birth weight (g) _____Present weight(g)_____

Breastfeeding: Yes □ (full __/ partial ___) No □

TSB:

At Enrolment_____Time_____DOL/HOL_____

After 4 hours_____
After 8 hours_____
After 12 hours_____
After 24 hours_____
After 36 hours_____
After 48 hours_____
After 60 hours_____
After 72 hours_____
After 84 hours_____
At discontinuing PT_____

Blood Grouping and Typing: Baby_____Mother_____

DCT_____

CBC WITH PS_____

Serum Sodium, At Enrolment_____
After 8 hours_____
After 24 hours_____
Blood Exchange Transfusion Required □
Not Required □

Diagnosis at discharge: _____

Date _____

Complications: No □ Yes □

Nature of Complications:_____

Comments:
_____

ABBREVIATIONS:

RCT = Randomized Controlled Trial

AGA = Appropriate for Gestational Age

TSB = Total Serum Bilirubin

BET= Blood Exchange Transfusion

DVET = Double Volume Exchange Transfusion

PT = Phototherapy

RBC = Red Blood Cell

UDPGT = Uridine Diphosphoglucuronosyl Transferase

ABE = Acute Bilirubin Encephalopathy

BIND = Bilirubin Induced Neurological Dysfunction

AAP = American Academy of Pediatrics

IVIG = Intravenous Immunoglobulin

IV = intravenous

EBM = Expressed Breast Milk

PATIENT INFORMATION SHEET

Title:

A Randomized Controlled Trial of Fluid Supplementation in Term Neonates with Severe Hyperbilirubinemia with N/3 (0.3%) saline in 5%Dextrose

Jaundice is a common problem in newborns. High levels of jaundice in babies can cause damage to the infant's brain. To prevent this phototherapy is the standard mode of treatment for jaundiced babies. In spite of phototherapy sometimes, jaundice does not come down and the baby requires an invasive procedure called blood exchange transfusion, which has its own inherent complications. There is a suggestion that breast fed babies given IV supplemental fluids and phototherapy can quickly cause decline in bilirubin and prevent blood exchange transfusion and hence its related complications. This study is to compare the efficacy of IV supplemental fluids and phototherapy when compared to phototherapy alone in preventing blood exchange transfusion.

Term neonates with high levels of non hemolytic jaundice with no signs of clinical dehydration after randomization shall be either given supplemental fluid therapy along with breast feeds at libitum while under standard phototherapy (interventional group) or only breast feeds at libitum while under standard phototherapy (control group). The primary and secondary outcomes will be studied in both the groups.

We would be happy if could make your baby a part of this study. We assure you that we would take utmost care to see that your baby is not harmed in any way throughout the study. A little amount of blood (around 2 ml) will be needed from your baby for biochemical investigations required to be done in the study. No harm will be rendered to your baby due to this.

There is no compulsion. You can withdraw from the trial at anytime during the study. Your baby will continue to receive routine care given to a jaundiced baby as per the hospital protocol. During the study, during the analysis of the results and during the publication of the study your identity will not be revealed.

The outcome of the study will be revealed to you after the completion of the study if requested for.

Signature of the Investigator Signature of Parent

Contact Address:

Dr. Mohamed Sajjid
D.M. Neonatology post graduate
I.C.H.&H.C, Egmore, Chennai- 8.
Mobile No.:9841318084.

Date :

Place : Chennai -8.

CONSENT FORM

Title:

A Randomized Controlled Trial of Fluid Supplementation in Term Neonates with Severe Hyperbilirubinemia with N/3 (0.3%) saline in 5%Dextrose

I Ms/Mr._____ M/O/F/O, B/O _____

Sex_____Hosp. No._____ admitted in ICH, Egmore on _____

was explained to by the doctor that my baby is being enrolled in fluid supplementation study for jaundice.

I have received the Patient Information Sheet from the doctor regarding the study

"I am willing for my child to be enrolled in fluid supplementation study for jaundice. The doctors have explained to me the nature and the purpose of the trial.

I have given my consent only after completely understanding the details that were explained to me.

I am willing for my baby to be enrolled in this study without any ones compulsion.

I am fully aware that I can withdraw from the trial at any time during the study and routine care will be continued.

I have given consent for usage of fluid supplementation for jaundice as per the study protocol.

I have also given my consent for drawing blood sample for biochemical analysis during the study if needed.

The rare complications which can arise was explained to me.

I have given this consent to be enrolled in this study with my full consciousness.

Signature of the Investigator **Signature of Parent**

Date :

Place: Chennai -8.

ஆராய்ச்சி தகவல் தாள்

பச்சிளம் குழந்தைகள் பொதுவாக மஞ்சள் காமாலை பாதிப்புக்கு ஆளாகும். தீவிர மஞ்சள் காமாலை குழந்தையின் மூளையை பாதிக்கக் கூடியது. பொதுவாக மஞ்சள் காமாலையை குறைப்பதற்காக போட்டோ தெரபி (ஒளிக் கதிர்) எனும் சிகிச்சை மேற்கொள்ளப்படும். ஆராய்ச்சியாளர்கள் நரம்பு வழியாக குளுக்கோஸ் செலுத்தி மஞ்சள் காமாலையை குறைக்க முடியுமா என முயன்று வருகின்றனர். இதன் தொடர்ச்சியாக பச்சிளம் குழந்தைகளுக்கு மஞ்சள் காமாலை பற்றி ஒரு ஆராய்ச்சி குழந்தைகள் நல மருத்தவமனையில் நடைபெற இருக்கிறது. இந்த ஆராய்ச்சியில் பச்சிளம் குழந்தைகள் இரு குழுக்களாக பிரிக்கப்பட்டு சிகிச்சைக்கு உள்ளாவார்கள். ஒரு பிரிவினருக்கு நரம்பு வழியாக குளுக்கோஸ் மற்றும் போட்டோ தெரபி (ஒளிக்கதிர்) கொடுத்தும், மற்றும் ஒரு பிரிவினருக்கு போட்டோ தெரபி (ஒளிக்கதிர்) மட்டுமே கொடுக்கப்படும். இரு பிரிவினருக்கும் தாய்ப்பால் கொடுக்கப்படும். குறிப்பிலாக்கம் முறையில் தேர்வு செய்யப்பட்டு உங்கள் குழந்தைக்கு ஏதேனும் ஒரு பிரிவில் உள்ள சிகிச்சை தரப்படும். குழந்தைக்கு மஞ்சள் காமாலை குறையும் வரை சிகிச்சைத் தரப்படும். மேலும் குளுக்கோஸ் ஏற்றும் பிரிவில் பக்கவிளைவுகள் வருமா என்பதனை ஆராய்ச்சி மூலம் கண்டறியப்படுகிறது.

உங்கள் குழந்தையும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியின் மூலம் உங்கள் குழந்தையின் நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பிற்கு ஏற்படாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களின் குழந்தையின் அடையாளங்களையோ அல்லது தங்களது மனைவியின் பெயரையோ (குழந்தையின் பெயரை) வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர்

மரு. முகமது சாஜித்

பச்சிளம் குழந்தைகள் பிரிவு

குழந்தைகள் நல மருத்துவமனை

எழும்பூர், சென்னை – 8.

செல் - 9841318084.

பங்கேற்பாளர் கையொப்பம்

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு : தீவிர மஞ்சள் காமாலையால் பாதிக்கப்பட்ட நிறை மாதம் ஆன குழந்தைகளுக்கு நரம்பு வாயிலாக குளுக்கோஸ் செலுத்துதல் மற்றும் போட்டோ தெரபி (ஒளிக்கதிர்) அல்லது போட்டோ தெரபி (ஒளிக்கதிர்) மட்டும் தரப்படும் சிகிச்சை தொடர்பான ஆராய்ச்சி.

பெயர்	:	தேதி	:
வயது	:	உள்நோயாளி எண்.	:
பால்	:	ஆராய்ச்சி சேர்க்கை எண்.	:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையா எனக்கு தெளிவாக விளக்கபட்டது. இதில் இரு குழுக்களாக பச்சிளம் குழந்தைகள் பிரிக்கப்படுவார்கள் என்பதை அறிந்தேன். இதில் ஏதேனும் ஒரு குழுவில் குறிப்பிலாக்கம் முறையில் எனது குழந்தை பங்கு கொள்வதில் நான் சம்மதம் தெரிவிக்கிறேன். எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சி பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியில் இருந்து எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

நான் பச்சிளங் குழந்தையின் மஞ்சள் காமாலை குறித்த இந்த ஆராய்ச்சியின் விவரங்களை கொண்ட தகவல் தாளை பெற்றுக் கொண்டேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் என் குழந்தையை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.

இந்த ஆராய்ச்சியில் எனது குழந்தைக்கு இரத்தம் எடுப்பதற்கு முழு சம்மதத்தை தெரிவித்து கொள்கிறேன். எனது குழந்தைக்கு ஆராய்ச்சியின் மூலம் ஏதேனும் பின் விளைவுகள் ஏற்படலாம் என மருத்தவர் மூலம் தெரிந்து கொண்டேன்.

தேதி கையொப்பம்

S NO.	NAME	GENDER	HOSPITAL	IM/EM	GROUP	MATERNAL AGE	GRAVIDA	PARA	LIVEBIRTHS	MATERNAL HTN	MATERNAL DM	MATERNAT APH	MATERNAL ANEMIA	AMNIOTIC FLUID	MODE OF DELV
1	B/O PADMAVATHY	2	1	1	2	25	2	2	2	2	2	2	2	1	VACUUM
2	B/O JEEVITHA	1	1	1	1	26	PRIMI		1	1	2	2	2	1	VAGINAL
3	B/O GOMATHI	2	1	1	1	20	2	2	2	2	2	2	2	1	VAGINAL
4	B/O SARITHA	1	1	1	2	25	2	2	2	2	2	2	2	1	ELECTIVE LSCS
5	B/O MONIKA	2	1	1	1	20	PRIMI		1	1	2	2	2	1	VAGINAL
6	BABY MITHUN	1	1	1	2	27	PRIMI		1	1	2	2	2	1	VAGINAL
7	BABY DEVIKA	2	1	1	2	20	PRIMI		1	1	2	2	2	1	VAGINAL
8	B/O YASERA BEGUM	1	1	1	1	27	2	2	2	2	2	2	2	1	VAGINAL
9	B/O HEMALATHA	2	1	1	2	19	PRIMI		1	1	2	2	2	1	ELECTIVE LSCS
10	B/O KUMARI TWIN 1	2	1	1	1	27	PRIMI		1	1	2	2	2	1	ELECTIVE LSCS
11	B/O THENMOZHI	1	1	1	1	19	PRIMI		1	1	2	2	2	1	VAGINAL
12	B/O BANUMATHI	2	1	1	2	26	PRIMI		1	1	2	2	2	1	VAGINAL
13	B/O REJI	1	1	1	2	24	2	2	2	2	2	2	2	1	ELECTIVE LSCS
14	B/O PANCHAVARNAM	2	1	1	2	26	2	1	1	2	2	2	2	1	ELECTIVE LSCS
15	B/O THILAGAM	1	1	1	2	27	PRIMI		1	1	2	2	2	1	VAGINAL
16	B/O SATHYA	1	1	1	1	21	2	2	2	2	2	2	2	1	VAGINAL
17	B/O PAPAATHI	1	1	1	1	27	PRIMI		1	1	2	2	2	1	ELECTIVE LSCS
18	B/O KAVITHA	2	1	1	2	24	PRIMI		1	1	2	2	2	1	VAGINAL
19	B/O SARANYA	2	1	1	1	20	PRIMI		1	1	2	2	2	1	VAGINAL
20	B/O LAKSHMI	2	1	1	2	26	3	3	3	2	2	2	2	1	VAGINAL
21	B/O BENAZEER	1	1	1	1	20	PRIMI		1	1	2	2	2	1	VAGINAL
22	B/O GUNAVATHY	1	2	2	1	32	PRIMI		1	1	2	2	2	1	VAGINAL
23	B/O KARPAGAM	1	1	1	2	23	2	2	2	2	2	2	2	1	ELECTIVE LSCS
24	B/O RAJESHWARI TWIN 2	2	1	1	1	25	PRIMI		1	1	2	2	2	1	ELECTIVE LSCS
25	B/O NAGAMMA	2	1	1	1	25	PRIMI		1	1	2	2	2	1	VAGINAL
26	B/O MYTHILI	2	2	2	2	24	2	2	2	2	2	2	2	1	ELECTIVE LSCS
27	B/O GEETHA	2	2	2	2	24	2	2	2	2	2	2	2	1	ELECTIVE LSCS
28	B/O BHAVANI	1	1	1	1	26	PRIMI		1	1	2	2	2	1	VAGINAL
29	B/O VAGITHA	2	1	1	2	26	2	2	2	2	2	2	2	1	VAGINAL
30	B/O NAGARANI	1	2	2	2	25	2	1	1	2	2	2	2	1	ELECTIVE LSCS
31	B/O RADHIKA	1	2	2	1	26	PRIMI		1	1	2	2	2	1	ELECTIVE LSCS
32	B/O SUGANYA	1	2	2	1	29	PRIMI		1	1	2	2	2	1	VAGINAL
33	B/O THENMOZHI	2	2	2	1	27	PRIMI		1	1	2	2	2	1	EMERGENCY LSCS
34	B/O BAKKIYALAXMI	2	1	1	2	21	PRIMI		1	1	2	2	2	1	VAGINAL
35	B/O KOMALAVATHY	1	1	1	2	27	PRIMI		1	1	2	2	2	1	EMERGENCY LSCS
36	B/O SUMITHRA	2	1	1	1	23	PRIMI		1	1	2	2	2	1	VAGINAL
37	B/O VASANTHI	1	1	1	1	19	PRIMI		1	1	2	2	2	1	VAGINAL
38	B/O GAYATHRI	2	2	2	2	26	2	2	2	2	2	2	2	1	ELECTIVE LSCS
39	B/O TAMILSELVI	2	2	2	1	25	2	2	2	2	2	2	2	1	ELECTIVE LSCS
40	B/O DHANALAKSHMI	2	2	2	1	24	3	2	2	2	2	2	2	1	VAGINAL
41	B/O SANGEETHA	1	2	2	2	25	PRIMI		1	1	2	2	2	1	VACUUM
42	B/O SHANTIPRIYA	2	2	2	2	20	PRIMI		1	1	2	2	2	1	OUTLET FORCEPS
43	B/O VASANTHI	2	2	2	2	25	PRIMI		1	1	2	2	2	1	ELECTIVE LSCS
44	B/O JUBETHA	2	1	1	1	23	2	2	2	2	2	2	2	1	VAGINAL
45	B/O GOWRI	2	2	2	2	24	PRIMI		1	1	2	2	2	1	EMERGENCY LSCS
46	B/O RADHIKA	2	2	2	1	20	PRIMI		1	1	2	2	2	1	VAGINAL
47	B/O SUGANYA	2	1	1	1	19	PRIMI		1	1	2	2	2	1	VAGINAL
48	B/O NASEEMA	1	2	2	1	22	PRIMI		1	1	1	2	2	1	VACUUM
49	B/O KANAGAVALLI	1	2	2	2	25	2	2	2	2	2	2	2	1	ELECTIVE LSCS
50	B/O BHUVANESWARI	1	2	2	1	23	PRIMI		1	1	2	2	2	1	EMERGENCY LSCS

S NO.	NAME	GENDER	HOSPITAL	IM/EM	GROUP	MATERNAL AGE	GRAVIDA	PARA	LIVEBIRTHS	MATERNAL HTN	MATERNAL DM	MATERNAT APH	MATERNAL ANEMIA	AMNIOTIC FLUID	MODE OF DELV
51	B/O SIVAMALA	1	2	2	2	30	3	2	2	2	2	2	2	1	ELECTIVE LSCS
52	B/O EZHILARASI	2	2	2	1	25	PRIMI	1	1	2	2	2	2	1	VAGINAL
53	B/O SHYAMALA	1	2	2	1	25	2	2	2	2	2	2	2	1	ELECTIVE LSCS
54	B/O AISHWARYA	2	1	1	2	22	PRIMI	1	1	2	2	2	2	1	ELECTIVE LSCS
55	B/O KALAIARASI	1	2	2	2	22	PRIMI	1	1	2	2	2	2	1	VAGINAL
56	B/O USHA	1	2	2	2	25	PRIMI	1	1	2	2	2	2	1	OUTLET FORCEPS
57	B/O PARVATHY	2	2	2	1	23	PRIMI	1	1	2	2	2	2	1	OUTLET FORCEPS
58	B/O ARCHANA	1	2	2	1	20	PRIMI	1	1	2	2	2	2	1	VAGINAL
59	B/O DEEPIKA	1	2	2	1	21	PRIMI	1	1	1	2	2	2	1	EMERGENCY LSCS
60	B/O JESSY	2	2	2	2	23	3	2	2	2	2	2	2	1	EMERGENCY LSCS
61	B/O RAJESWARI	1	2	2	2	26	PRIMI	1	1	1	2	2	2	1	EMERGENCY LSCS
62	B/O MUTHULAKSHMI	2	1	1	2	29	PRIMI	1	1	2	2	2	2	1	EMERGENCY LSCS
63	B/O RAJESHWARI	1	2	2	1	26	PRIMI	1	1	2	2	2	2	1	LMC FORCEPS
64	B/O RAJALAXMI	2	1	1	1	24	2	2	2	2	2	2	2	1	VAGINAL
65	B/O AMUDHA PAULIN	1	1	1	2	23	PRIMI	1	1	2	2	2	2	1	ELECTIVE LSCS
66	B/O SANDHIYA	1	1	1	2	25	3	3	3	2	2	2	2	1	VAGINAL
67	B/O PRIYA	2	2	2	1	23	PRIMI	1	1	2	1	2	2	1	VAGINAL
68	B/O CHANDRA	2	2	2	2	25	PRIMI	1	1	2	2	2	2	1	VAGINAL
69	B/O AMEENA BEE	1	2	2	2	27	PRIMI	1	1	1	2	2	2	1	VAGINAL
70	B/O YAMUNA	2	2	2	1	22	3	3	2	2	2	2	2	1	VAGINAL
71	B/O ELLAMMAL	1	2	2	2	26	PRIMI	1	1	2	2	2	2	1	VAGINAL
72	B/O GOVINDAMMAL	1	2	2	1	24	2	1	1	2	2	2	2	1	VACUUM
73	B/O VINNARASI	1	2	2	1	19	PRIMI	1	1	2	2	2	2	1	VAGINAL
74	B/O KAVITHA	1	1	1	2	24	PRIMI	1	1	2	2	2	2	1	VAGINAL
75	B/O KARPAGAVALLI	2	1	1	1	23	2	2	2	2	2	2	2	1	ELECTIVE LSCS
76	B/O POORNIMA	1	1	1	1	26	2	2	2	2	2	2	2	1	VAGINAL
77	B/O DEVI	2	1	1	2	22	3	3	3	2	2	2	2	1	VAGINAL
78	B/O REVATHY	1	1	1	2	27	PRIMI	1	1	2	2	2	2	1	VAGINAL
79	B/O NITHYA	1	1	1	2	22	2	2	2	2	2	2	2	1	VAGINAL
80	B/O CHITRA	2	1	1	1	26	3	3	3	2	2	2	2	1	VAGINAL
81	B/O LATHIKA	2	1	1	1	22	PRIMI	1	1	2	2	2	2	1	VAGINAL
82	B/O RAMANI	1	1	1	2	26	PRIMI	1	1	2	2	2	2	1	OUTLET FORCEPS
83	B/O MUNIYENDRA	1	1	1	1	21	PRIMI	1	1	2	2	2	2	1	EMERGENCY LSCS
84	B/O SUMATHI	1	1	1	2	27	PRIMI	1	1	2	2	2	2	1	VAGINAL

GA	BW	PW	% WT LOSS	BF	AGE ONSET	AGE INCL	TSB 0 HRS	TSB 4 HRS	% FALL 4 HRS	TSB 8 HRS	% FALL 8 HRS	TSB 24 HRS	% FALL 24 HRS	BET	PT DURATION
40.6	2600	2510	3.5	1	3	4.7	22.8	19.8	13	17	25	14.8	35	2	24
38.7	3250	2990	8	1	4	4.7	25	19.5	22	16.5	34	13	48	2	24
38	2700	2500	7.4	1	3	7.5	24.2	18.9	22	18	25	14.1	41	2	24
39.8	3016	3000	0.5	1	4	4.5	25	27	NA	NA	NA	NA	NA	1	NA
38.4	2500	2400	4	1	3	3.5	21.6	17.8	17	16.8	22	12.3	43	2	24
38	2600	2500	3.8	1	4	7.5	21.5	23.5	NA	NA	NA	NA	NA	1	NA
38	2500	2400	4	1	3	9.5	20.7	16.4	20	16.4	20	16.3	21	2	48
40	2750	2720	1	1	3	3.5	22.2	16.5	25	16.5	25	15.9	28	2	36
39.8	3000	2830	5.7	1	1.5	2	23.3	23	1	23	NA	NA	NA	1	NA
39	2500	2260	9.6	1	3	3.5	24.8	28	NA	NA	NA	NA	NA	1	NA
40	3750	3720	0.8	1	3	3.5	23.4	22.6	3	22	6	14.8	36	2	36
38	3600	3320	7.7	1	3	6.5	23.6	26.4	NA	NA	NA	NA	NA	1	NA
38.8	2700	2400	11	1	2	3.3	20.5	19	7	14.6	28	14	31	2	36
40.3	2860	2800	2	1	2	3.5	21	23.8	NA	NA	NA	NA	NA	1	NA
38.8	2900	2720	6.2	1	1.5	2.2	20.1	22.1	NA	NA	NA	NA	NA	1	NA
38	3250	3200	1	1	3	4.5	23.8	19.2	19	18.1	24	15.8	33	2	36
38	3250	3000	7.7	1	2	3	23.7	21.4	9	18	24	14	41	2	24
39.8	2660	2630	1.1	1	4	5.5	20.2	19	6	18.1	11	15.1	25	2	24
40.4	2500	2300	8	1	3	5.5	20.3	18	11	16.8	17	15	26	2	24
40	3000	2850	5	1	4	5.5	25	27.6	NA	NA	NA	NA	NA	1	NA
38	2600	2400	7.7	1	3	5.9	20.8	18.5	11	16.6	20	11.8	43	2	24
38	2900	2700	6.9	1	1.5	2	20.2	18	10	16.8	17	12.3	39	2	24
39.8	2750	2650	3.6	1	2	3	22.5	20.5	8	19.6	9	12.3	45	2	24
38	2500	2250	10	1	4	5	20.1	18.1	10	16.8	16	14.1	30	2	24
39.3	3000	2900	3.3	1	5	6.5	23.9	20.4	14	20.4	14	15.8	34	2	36
39	3250	3060	5.8	1	3	4.5	22.5	21	6	19	15	15	33	2	36
39	3250	2990	8	1	4	5	20.6	19	8	17.8	13	14	32	2	24
38	3250	2990	8	1	2	2.2	20.8	17	18	16.5	20	14.8	29	2	24
40	3100	3030	2.2	1	3	3.5	21.8	20	8	18	17	14	36	2	24
39.4	3500	3245	7.2	1	2	2.9	20.2	22.5	NA	NA	NA	NA	NA	1	NA
38	2750	2630	4	1	4	6.5	20.8	19.5	6	18.1	18	14.8	29	2	24
38.7	2800	2700	3	1	3	4.5	22.1	20.1	9	19	14	9.6	56	2	24
38	2700	2485	8	1	1.5	2	20.1	19	5	17.8	11	13.5	33	2	24
39.7	3250	2960	9	1	5	6.5	24.1	23.8	1	24.1	NA	NA	NA	1	NA
40	2700	2530	5	1	2	2.6	25	24	4	25	NA	NA	NA	1	NA
38.4	2750	2550	7	1	3	3.5	22.1	18	18	16	28	13.8	37	2	24
38.6	2500	2250	10	1	4	7.5	24.2	19.8	18	16.8	30	12	50	2	24
38	2600	2395	7.9	1	3	4	20.1	19	5	18.5	8	12.5	37	2	36
38	2500	2250	10	1	3	5.5	20.1	18.1	10	16.8	16	13.3	34	2	24
39	3200	3100	3.1	1	1.5	2	23.8	18.1	24	16.1	32	12	49	2	24
38	2700	2650	1.8	1	2	2.8	20.4	19.8	3	18.5	9	15	26	2	36
39.3	3105	2860	7.9	1	3	4	20.1	18.4	8	16.8	16	13	35	2	24
38.4	2700	2450	9.2	1	3	4.5	21.3	20	6	18.8	12	15.8	26	2	36
40	3060	3000	1.9	1	1.5	1.9	20.4	18	12	17	17	13	36	2	24
40	2500	2400	4	1	2	3	20.7	19	8	18.1	12	10	52	2	24
40	3200	3130	2.2	1	4	8.5	22.1	18	18	13.8	37	12	46	2	12
38	2500	2440	2.4	1	4	6.5	24.4	22.2	9	17.8	27	15	38	2	36
38.4	3500	3300	5.7	1	3	4	20.1	18.8	6	18	10	14.1	30	2	24
38.3	2500	2250	10	1	3	4.5	25	23.8	5	26.4	NA	NA	NA	1	NA
41	3800	3690	2.9	1	3	3.5	21.8	20.1	8	17	22	9	59	2	24

GA	BW	PW	% WT LOSS	BF	AGE ONSET	AGE INCL	TSB 0 HRS	TSB 4 HRS	% FALL 4 HRS	TSB 8 HRS	% FALL 8 HRS	TSB 24 HRS	% FALL 24 HRS	BET	PT DURATION
38	2700	2480	8.1	1	4	6.5	24.6	23	6	21.8	11	17	31	2	48
38	3690	3375	8.5	1	3	5.5	20.3	18.1	11	16	21	15	26	2	12
38	3300	2995	9.2	1	3	4.5	22	20	9	18	18	14	36	2	24
40	3200	2990	6.6	1	2.5	3.5	25	24	4	26.7	NA	NA	NA	1	NA
38	2500	2300	8	1	3	4.5	22	20.8	5	19	14	15	32	2	36
38	2500	2400	4	1	3	3.5	20.1	19.9	1	18.1	10	14	30	2	24
40	2500	2300	8	1	2	3.5	24.2	21	13	19.6	19	14	42	2	24
38	2900	2710	6.5	1	3	4	21.2	19.1	10	16.7	21	14.1	33	2	24
39	3100	2980	3.9	1	2	3.5	20.6	18	13	16.8	18	14	32	2	24
39.8	2750	2600	5.4	1	2	3.5	25	23.8	5	21.9	12	17	32	2	48
38.3	2600	2435	6.3	1	2	3.5	20.7	18.7	10	17	18	14	32	2	24
38	2500	2350	6	1	3	4.5	23.4	23	2	23	NA	NA	NA	1	NA
38	2700	2500	7.4	1	3	4.5	21.3	20	6	18	15	14.2	33	2	24
38	2530	2300	9	1	2	3.5	22.6	20.9	7	18.7	17	17.4	23	2	48
39.3	3480	3400	2.3	1	3	4.7	25	24	4	24	NA	NA	NA	1	NA
38.3	3500	3200	8.5	1	3	4	23.4	22.4	4	23.4	NA	NA	NA	1	NA
38	3530	3230	8.5	1	4	5	25	23	8	20	20	15	40	2	36
39	2940	2850	3	1	3.5	4.5	22	21	4	19.8	10	13.4	39	2	36
40.3	3110	2905	6.6	1	2	3	20.3	19	6	18	11	15	26	2	36
39.7	2750	2600	5.4	1	3	5.2	25	23.1	8	20	20	13	48	2	36
40.3	2750	2590	5.8	1	2	2.9	25	24.6	2	28	NA	NA	NA	1	NA
38	2600	2350	9.6	1	4	5	20.1	18.1	10	16.4	18	12	40	2	24
39	2870	2790	2.8	1	3	4.5	23.2	18.4	21	18.4	21	15.2	34	2	24
38	2750	2500	9	1	3	3.5	20.6	19	8	17.8	13	14	32	2	24
40	2800	2730	2.5	1	2.5	3.2	20.9	18.2	13	16.8	20	14	33	2	24
40	3200	3050	4.7	1	4	5	20.8	18	15	16.8	19	13	37	2	24
40	3400	3100	8.8	1	4	6.5	20.8	18.1	13	16.5	21	14	33	2	24
38	3200	3010	5.9	1	3	4.8	20.5	20	2	22.5	NA	NA	NA	1	NA
38.3	3000	2830	5.7	1	3	4.5	20.3	20.1	1	18.1	10	12.4	39	2	36
39.6	3050	2920	4.3	1	3	4.5	20.2	18.1	10	17	16	14	31	2	24
39	2750	2600	5.4	1	4	6.5	20.4	18.2	11	16.6	19	14	31	2	24
39	2500	2340	6.4	1	3	4.5	20.2	18.8	7	17	16	11.7	42	2	24
39.1	2500	2440	2.4	1	2.5	3.7	20.7	18.1	12	16.8	19	10.5	49	2	24
38	2500	2360	5.6	1	3	4.5	20.8	18.8	10	16.9	19	13	37	2	24

BABY BG	BABY TYPE	MOTHER BG	MOTHER TYPE	DCT	HEMATOCRIT	% RC	SS 0HRS	SS 8 HRS	SS 24 HRS	COMPLICATIONS
2	1	2	1	2	46.1	2	152	153	150	2
2	1	2	1	2	45.7	2	153	152	150	2
2	1	1	1	2	41.1	2	139	140	139	2
1	1	1	1	2	41	2	137	145	140	2
2	1	1	1	2	42	3	145	150	145	2
1	1	1	1	2	50.5	2	141	153	145	2
1	1	3	1	2	49	3	141	148	145	2
2	1	1	1	2	45	2	136	145	142	2
2	1	1	1	2	43.5	5	146	148	148	2
3	1	1	1	2	42	2	144	138	140	2
3	1	1	1	2	44.7	3	145	143	140	2
3	1	2	1	2	48	2	139	140	141	2
1	1	1	1	2	43	5	143	145	144	2
3	1	1	1	2	42.1	1	147	146	140	2
2	1	1	1	2	49.6	1	151	149	145	2
2	1	1	1	2	52	2	147	148	145	2
3	1	3	2	2	53	3	136	135	135	2
1	1	1	1	2	45	4	144	140	139	2
1	1	1	1	2	45	2	141	142	144	2
1	1	1	1	2	45	2	143	145	145	2
3	1	3	1	2	50.5	2	146	148	145	2
1	2	2	1	2	44	2	141	145	144	2
3	1	3	1	2	53	2	142	141	143	2
4	1	4	1	2	49.7	2	144	145	142	2
1	1	1	1	2	51	2	144	142	143	2
1	1	1	1	2	49.7	2	145	144	142	2
3	1	3	1	2	50	3	138	140	141	2
3	1	1	1	2	47	4	144	145	145	2
3	1	4	1	2	42	3	145	144	139	2
1	1	1	1	2	41.9	2	145	144	142	2
2	1	1	2	2	52	2	140	145	143	2
1	1	1	1	2	44	2	140	145	142	2
3	1	1	2	2	42	3	138	144	140	2
1	1	1	2	2	43.9	2	145	139	140	2
3	1	1	1	2	50.5	2	148	145	144	2
1	1	3	1	2	46	2	135	145	140	2
1	1	3	1	2	48	2	144	145	144	2
3	1	3	2	2	45	3	138	140	141	2
1	1	1	1	2	45	3	144	145	144	2
2	1	1	1	2	45	2	140	145	138	2
2	1	2	1	2	47.7	2	140	142	141	2
1	1	1	2	2	50	2	140	141	142	2
2	1	2	1	2	53	1	140	141	142	2
1	1	1	1	2	48	5	141	140	142	2
2	1	1	1	2	42	2	138	140	142	2
3	1	1	1	2	44.9	2	144	145	138	2
1	1	1	1	2	41	2	146	145	145	2
1	1	2	1	2	50.2	1	140	142	140	2
2	1	1	1	2	42.6	3	145	144	143	2
4	1	3	1	2	48	1	140	141	142	2

BABY BG	BABY TYPE	MOTHER BG	MOTHER TYPE	DCT	HEMATOCRIT	% RC	SS 0HRS	SS 8 HRS	SS 24 HRS	COMPLICATIONS
4	1	4	1	2	50.4	2	145	144	143	2
3	1	1	1	2	43.3	2	140	144	138	2
1	1	1	1	2	42.1	2	139	144	140	2
3	1	1	1	2	45.8	2	146	144	145	2
4	1	4	1	2	50.8	2	145	144	140	2
1	1	1	1	2	45	2	140	138	143	2
1	1	1	1	2	45	3	138	145	140	2
2	1	2	1	2	45	1	139	144	142	2
1	1	1	1	2	42.1	2	138	139	140	2
2	1	1	1	2	44.6	2	145	142	144	2
2	1	1	1	2	45	2	145	144	140	2
2	1	1	1	2	47	2	145	140	138	2
1	1	1	1	2	50.9	2	140	145	143	2
2	1	1	1	2	48.8	3	142	140	140	2
2	1	1	1	2	47.7	2	139	140	138	2
2	1	1	1	2	43.8	1	140	138	135	2
3	1	3	1	2	45	2	138	140	142	2
3	1	3	1	2	50	1	145	140	141	2
2	1	2	1	2	45	2	138	140	139	2
2	1	3	1	2	46.9	2	138	140	140	2
3	1	1	1	2	50	2	136	138	140	2
1	1	1	1	2	53	1	140	141	139	2
3	1	3	1	2	52	2	138	141	140	2
1	1	1	1	2	53.5	1	145	144	144	2
2	1	1	1	2	45	2	146	150	145	2
3	1	3	1	2	45	3	145	145	140	2
3	1	1	1	2	44	2	150	148	145	2
1	1	1	1	2	41.1	2	152	144	140	2
2	1	1	1	2	47.9	2	149	146	145	2
1	1	1	1	2	45	1	140	145	140	2
1	1	1	1	2	41	2	144	145	142	2
1	1	1	1	2	45	3	160	161	151	2
2	1	1	1	2	50	2	150	148	145	2
1	1	1	1	2	45	2	143	138	140	2